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CURRENT OPINION

Is sunlight good for our heart?

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Introduction

Humans evolved being exposed for about half of the day to the light of the sun. Nowadays, exposure to sunlight is actively discouraged for fear of skin cancer, and contemporary lifestyles are associated with long hours spent under artificial light indoors. Besides an increasing appreciation for the adverse effects of these life-style-related behavioural changes on our chronobiology, the balance between the beneficial and harmful effects of sunlight on human health is the subject of considerable debate, in both the scientific and popular press, and the latter is of major public health significance. While there is incontrovertible evidence that ultraviolet radiation (UVR) in the form of sunlight is a significant predisposing factor for non-melanoma and melanoma skin cancers in pale skinned people,[1] a growing body of data suggest general health benefits brought about by sunlight.[2] These are believed to be mediated either by melatonin or vitamin D. Melatonin is produced from serotonin by the pineal gland located in the centre of the brain during periods of darkness, and its release is suppressed as a function of the visible light intensity sensed through ocular photoreceptors. Vitamin D is formed by ultraviolet B (UVB)-mediated photolysis of 7-dehydrocholesterol in the skin. Both melatonin and vitamin D are pleiotropic hormones that exert a multitude of cellular effects by interacting with membrane and nuclear receptors, and receptor-independent actions. People with more heavily pigmented skin require higher doses of UVB to produce adequate amounts of vitamin D, and this may have been an evolutionary driver to the variation of human skin colour with latitude and intensity of solar irradiation. Our degree of exposure to sunlight is easily modified by behavioural factors such as the use of clothing, sunglasses, and sun-blocking creams, and time spent outdoors. Balancing the carcinogenic risks with the requirement for vitamin D has led to advice on moderating sun exposure, while supplementing food with vitamin D. Guidance on such behaviour is part of the public health campaigns in most countries with Caucasian populations. Following these suggestions, we may, however, be missing out on other health benefits provided by natural sunlight that are less obvious and unrelated to the above classical mediators.

Core hypothesis

We propose here that many of the beneficial effects of sunlight, particularly those related to cardiovascular health, are mediated by mechanisms that are independent of melatonin, vitamin D, and exposure to UVB alone. Specifically, we suggest that the skin is a significant store of nitric oxide (NO)-related species that can be mobilized by sunlight and delivered to the systemic circulation to exert coronary vasodilator and cardioprotective as well as antihypertensive effects (*Figure 1*). We further hypothesize that this dermal NO reservoir is a product of local production and dietary supply with nitrate-rich foods.

Sunlight and cardiovascular disease

The roots of photomedicine are ancient, dating back to the beginnings of civilization when heliotherapy was found to improve certain disease states. Sunlight was observed to have cardiovascular effects during the MRC hypertension trials of the 1970s with blood pressure being consistently lower in summer than winter.[3] The prevalence of hypertension and mean population diastolic and systolic blood pressures correlate directly with latitude, being higher in populations living further from the equator.[4] This may be due to a number of racial and environmental factors other than sunlight. Yet, within the UK, all-cause mortality (of which the major cause is ischaemic heart disease) correlates linearly with latitude (relative risk 1.0 at 50°N, 1.46 ± .03 at 55°N), even after accounting for all known risk factors and possible protective variables such as fruit and vegetable consumption.[5] Moreover, following migration, the mortality risk changes to that of

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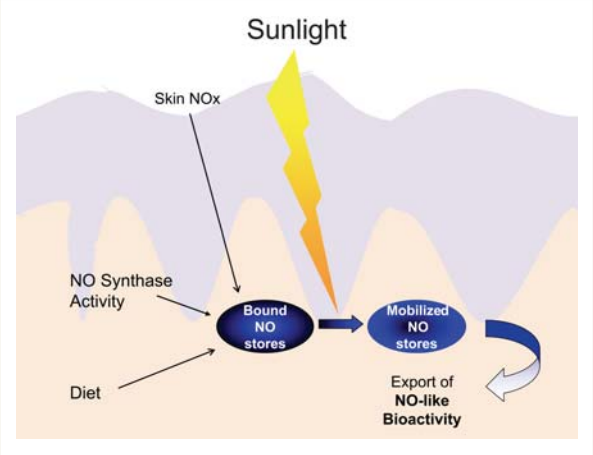

Figure 1 Sunlight-induced export of nitric oxide bioactivity from storage forms in the skin.

the new place of residence.[6] Seasonal variations in light intensity, caused by the inclination of the Earth's rotary axis (contrary to common belief, the intensity of solar radiation is not governed by the distance between Earth and sun; paradoxically, our planet is closest to the sun in winter, not summer), are accompanied by seasonal variations in incidence and mortality of cardiovascular disease (CVD). Similar to stroke, rates of acute coronary syndromes (including unstable angina, acute myocardial infarction, atrial fibrillation, and sudden cardiac death) are highest in the winter months with shorter hours of daylight.[7] Temperature stress and sympathetic activation have been suggested as a cause for this, but the same effect is seen in countries such as Kuwait, where temperatures in winter are most comfortable and impose least physiological stress.[8] Sunlight exposure in temperate climates is markedly reduced in winter not only because of the reduction in daylight hours, but also because of increased light-impenetrable clothing worn.

Recent findings and possible impact on cardiovascular disease burden

Recently, Suschek and co-authors[9] demonstrated that irradiation of healthy individuals with biologically relevant doses of UVA leads to a sustained reduction in blood pressure. This is an important finding as small changes in population blood pressure can produce significant reductions in deaths from cerebral and coronary vascular disease. The fall in mortality due to stroke, ischaemic heart disease, and other vascular diseases is directly and linearly proportional to the degree of reduction in blood pressure, and a 20 mmHg lower systolic blood pressure leads to a two-fold reduction in overall mortality in both men and women aged 40–69 years.[10] These dramatic effects on major causes of morbidity and mortality highlight the benefits expected from even small UV-mediated reductions in blood pressure. Besides their positive impact on the burden of disease from a human, family, and societal perspective, moderate exposure to sunlight may also reduce the economic burden of CVD. The latter has been estimated to amount to €169 billion annually for the European Union[11] and $519 billion for hypertension, heart disease, and stroke in the USA[12] (combined impact of healthcare costs and lost economic output in 2003). Thus, even minor reductions in blood pressure due to enhanced exposure to sunlight could translate into hundred thousands of person-years of life and billions of dollars and Euros saved every year.

What mechanisms may be involved and what other effects can be expected from moderate exposure to sunlight?

Nitric oxide, produced from L-arginine by nitric oxide synthase (NOS) in the endothelium, has been recognized as a key vasodilator in the vascular system since the identification of EDRF as NO,[13] and systemic inhibition of NO formation is accompanied by an immediate rise in blood pressure. *In vivo*, NO is rapidly inactivated by reaction with oxygenated haemoglobin and reactive oxygen species, giving rise to the formation of nitrate (NO_3^-), nitrite (NO_2^-), and several reactive nitrogen oxide species. The short half-life of NO should prevent it from having major actions at a distance from its site of production, although conversion to longer-lived species with vasodilator properties is known to occur in the circulation.[14] Nitrite, for long considered biologically inert at low concentrations, is now known not only to dilate blood vessels in its own right but to also protect organs against ischaemia/reperfusion (I/R) damage (reviewed in ref.[15,16]). Haemoglobin, myoglobin, xanthine oxidoreductase, cytochrome P-450, and mitochondrial enzymes can all generate NO from nitrite, in particular under hypoxic conditions. Apart from continuous enzymatic NO production, blood vessels 'photorelax' on direct irradiation with UVA, and this effect is potentiated in the presence of sodium nitrite.[17] Endogenous nitrite and S-nitrosothiols (RSNOs) in the vasculature have been shown to account for this phenomenon, and both compounds have absorption peaks within the UVA wavelength range.[18] Similarly, UVA irradiation of skin *in vitro* leads to photodecomposition of 'NO stores' and release of NO.[19] By weight, the skin is one of the largest organs in the body, with a surface area of around 2 m^2 in the average adult. All three NOS isoforms are expressed in the dermis and epidermis,[20] and in addition to this, nitrite and NO are generated on the skin surface by reduction of sweat nitrate[21] and possibly by the oxidation of ammonia[22] (*Figure* 2). The epidermis is particularly rich in cysteine-containing proteins and their sulfhydryl groups are readily nitrosated to form RSNOs. Nitrite, nitrate, and RSNOs are found in the dermis and epidermis at concentrations one or two orders of magnitude higher than those in plasma.[19,23] In adults, skin and blood are of comparable weight and volume, and nitrite in the epidermis alone amounts to ~135 μmoles, while total nitrite in blood rarely exceeds 13–15 μmoles.[23] Thus, mobilization of only a fraction of the relatively large epidermal pool of e.g. nitrite by sunlight is likely sufficient to transiently increase

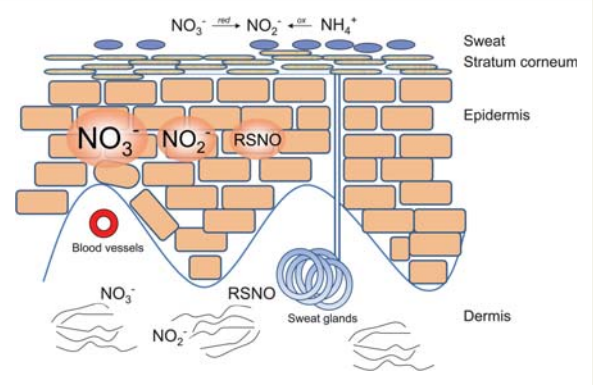

Figure 2 Enzymatic and non-enzymatic sources and location of major nitric oxide-related biomolecules in the skin.

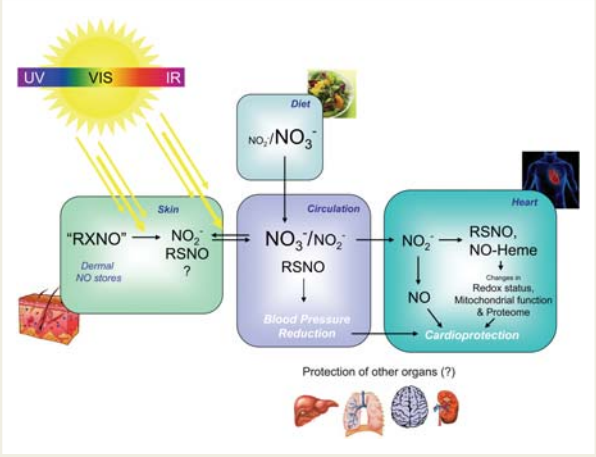

Figure 3 Possible molecular mechanisms involved in mediating the beneficial cardiovascular effects of sunlight.

plasma nitrite concentrations. The exact mechanism of release and nature of the dermal 'NO stores' is unknown (in addition to the species discussed above it may include metal nitrosyls such as dinitrosyl iron complexes and NO-haem species), but increases in systemic nitrite availability would rapidly translate into higher concentrations of nitroso products in blood and tissues,[24] and this is likely to contribute to cytoprotection and vasodilatation. A recent human study has demonstrated that UVA irradiation can increase plasma nitrite levels by 40%.[9] This is intriguing considering that in animal models, a similar increase in nitrite is associated with cardioprotection following I/R injury.[25] Dietary nitrate intake (predominantly from green leafy vegetables) may provide an alternative source of nitrite. An entero-salivary circulation of nitrate ensures that part of this dietary nitrate is reduced to nitrite by facultative anaerobic bacteria in the mouth. Thus, a high nitrate meal leads to a sustained increase in circulating nitrite,[26] and this nitrite increase is paralleled by reduction in systemic blood pressure suggesting further reduction to NO.[27,28] In addition to the commensal bacterial flora, mammalian tissues are endowed with the capacity of sequential nitrate → nitrite → NO reduction.[29] Skin bound NO stores are in equilibrium with circulating nitrite in unirradiated individuals,[23] and dietary-derived nitrite may therefore 'top up' the skin reservoir. In addition, circulating nitrate may be photolysed by UVA reaching the superficial dermal vasculature and give rise to the formation of NO, nitrite, and nitroso species.[30] Thus, multiple processes in the skin and in the circulation may contribute to light-induced blood pressure reduction and cardioprotection, with changes in nitrite and nitroso species concentrations playing key roles (*Figure 3*). Lower levels of sunlight reaching the skin during the winter season may translate into lower nitrite and nitroso species concentrations in the skin and circulation, and this may contribute to seasonal variations in CVD. Unfortunately, little is known about seasonal differences in NO-related species concentrations; no data are available on nitroso species variations and information about circulating nitrite/nitrate levels is conflicting,[31,32] possibly due to confounding nutritional influences.

Even small bursts in systemic nitrite levels can have profound effects on cardiac redox status and trigger long-lasting changes in abundance and post-translational modification (including oxidation, nitrosation, nitrosylation, nitration, and phosphorylation) of a large number of proteins.[33] The magnitude and breadth of nitrite-induced changes to the cytosolic and mitochondrial cardiac proteome is rather surprising and includes enzymes involved in metabolism, energy production, redox regulation, contractile function, and serine/threonine kinase signaling[33] as well as effects on complex I of the respiratory chain.[34] Some alterations are reminiscent of ischaemic preconditioning and consistent with a cardioprotective phenotype, although the overall complexity of changes observed suggest involvement of additional mechanisms. To this end, nitrite has recently been shown to affect T- cell function and cytokine release,[35] raising the possibility that it may also affect inflammatory processes. Effects of nitrite and nitroso products on inflammation and immune cell function would be of obvious significance for CVD, and a systemic increase in circulating nitrite following whole body exposure to UVR may account for the well-known effects of sunlight on the immune system. The situation is likely to be even more complex as both, melatonin and vitamin D, are known to affect the formation and availability of NO at multiple levels, providing ample opportunity for cross-talk between these pathways. Although nitrite would seem to be a likely source and nitroso species possible mediators of the effects of sunlight on blood pressure, the processes conferring cardioprotection may well involve additional metabolic pathways and signalling processes. Which NO metabolite ultimately accounts for what biological effect is currently unclear and elucidation of the pathways involved in local and systemic responses to sunlight will require further investigation. Nevertheless, it would appear that enhancing the availability of NO-related metabolites by sunlight has the potential to confer cardiovascular protective effects not afforded by other mediators typically associated with exposure to sunlight. Some of the effects described here may not be limited to the heart but provide benefit for other organ systems as well (*Figure 3*).

Hypothesis testing and outlook

Hypertension and ischaemic heart disease are major causes of morbidity and mortality, particularly in northern Europe, but excessive sun exposure carries significant risks. It appears challenging to appropriately measure and quantify sunlight exposure, evaluate its weighted relevance compared with overt traditional risk factors, and establish its actual relationship with vascular function and endothelial function. However, if proven correct, our hypothesis will have major implications for public health advice. If true, we would expect to find an inverse correlation between markers of sun exposure, such as actinic keratoses and skin cancers and prevalence of hypertension, ischaemic heart disease, and stroke. Such relationships can be investigated by interrogation of population diagnostic databases. Differentiating the effects of sunlight on cardiovascular and hypertensive mortality will require careful stratification for expected confounding variables associated with differing sun exposure patterns, and data on these factors (e.g. smoking history, diet, and social class) will need to be available. At the experimental level, we need a better understanding of precisely how different wavelengths of the electromagnetic solar radiation interact with NO-related species and what the subsequent fate of the reaction products is. Of note, also near-infrared and infrared light, which penetrate skin to reach much deeper tissue layers compared with UV, can release NO from nitrosyl-haem species.[36] Thus, light of various wavelengths—perhaps even visible light—may affect NO status, provided overall photic energy levels are sufficient for the mobilization of dermal NO stores. We also need to measure the dose-response relationship of sunlight's effects on blood pressure and other cardiovascular parameters such as coronary and systemic vascular distensibility and total peripheral resistance. This and other information will be crucial to identify how much of an NO-related pool of mediators is required to enable sunlight to have its proposed cardiovascular effects, and whether this pool is skin-bound, or present in the superficial dermal vasculature. The stage of life at which UV exposure occurs may be significant. Episodic sunburn in childhood is a particular risk factor for malignant melanoma, the most serious of the UV-related skin cancers. The most marked effect of seasonal variation in blood pressure is seen in older age cohorts.[3] Cardiovascular mortality of individuals who moved relates to the geographical destination, not the childhood origin of the migrant subjects.[6] The adult cardiovascular system may thus be more susceptible to the beneficial effects of sunlight-related NO release than that of children. Considering the demographic transition to an ageing world population with enhanced CVD risk, this differentiation may be significant. If confirmed, it will enable public health messages to be tailored to cautious sunlight exposure in childhood, with increased exposure later in life, to limit the carcinogenic effects of sunlight on the skin early on, while allowing full benefit to be obtained from its cardiovascular effects later. In conclusion, harnessing the power of the sun for our health may not stop at the production of melatonin and vitamin D, but include pathways under control of NO and nitrite/nitrate. Irrespective of the precise mechanism(s) of action, a modulation (e.g. by dietary measures) of the NO-related store in the skin and cautious bodily exposure to sunlight would seem to provide cardiovascular benefits. The future is bright—let a little sunshine into your heart.

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References

1. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol* 2008;**58**(Suppl. 2):S129–S132.
2. Moan J, Porojnicu AC, Dahlback A, Setlow RB. Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure. *Proc Natl Acad Sci USA* 2008;**105**:668–673.
3. Brennan PJ, Greenberg G, Miall WE, Thompson SG. Seasonal variation in arterial blood pressure. *Br Med J (Clin Res Ed)* 1982;**285**:919–923.
4. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997;**30**:150–156.
5. Law MR, Morris JK. Why is mortality higher in poorer areas and in more northern areas of England and Wales? *J Epidemiol Community Health* 1998;**52**:344–352.
6. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Migration within Great Britain and cardiovascular disease: early life and adult environmental factors. *Int J Epidemiol* 2002;**31**:1054–1060.
7. Kloner RA, Poole WK, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. *Circulation* 1999;**100**:1630–1634.
8. Douglas AS, al Sayer H, Rawles JM, Allan TM. Seasonality of disease in Kuwait. *Lancet* 1991;**337**:1393–1397.
9. Oplander C, Volkmar CM, Paunel-Gorgulu A, van Faassen EE, Heiss C, Kelm M, Halmer D, Murtz M, Pallua N, Suschek CV. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. *Circ Res* 2009;**105**:1031–1040.
10. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
11. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J* 2006;**27**:1610–1619.
12. Devol R, Bedroussian A. *An Unhealthy America: The Economic Burden of Chronic Disease—Charting a New Course to Save Lives and Increase Productivity and Economic Growth*. Milken Institute; 2007.
13. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;**327**:524–526.
14. Rassaf T, Preik M, Kleinbongard P, Lauer T, Heiss C, Strauer BE, Feelisch M, Kelm M. Evidence for in vivo transport of bioactive nitric oxide in human plasma. *J Clin Invest* 2002;**109**:1241–1248.
15. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat Rev Drug Discov* 2008;**7**:156–167.
16. Butler AR, Feelisch M. Therapeutic uses of inorganic nitrite and nitrate: from the past to the future. *Circulation* 2008;**117**:2151–2159.
17. Matsunaga K, Furchgott RF. Interactions of light and sodium nitrite in producing relaxation of rabbit aorta. *J Pharmacol Exp Ther* 1989;**248**:687–695.
18. Rodriguez J, Maloney RE, Rassaf T, Bryan NS, Feelisch M. Chemical nature of nitric oxide storage forms in rat vascular tissue. *Proc Natl Acad Sci USA* 2003;**100**:336–341.
19. Paunel AN, Dejam A, Thelen S, Kirsch M, Horstjann M, Gharini P, Murtz M, Kelm M, de Groot H, Kolb-Bachofen V, Suschek CV. Enzyme-independent nitric oxide formation during UVA challenge of human skin: characterization, molecular sources, and mechanisms. *Free Radic Biol Med* 2005;**38**:606–615.
20. Bruch-Gerharz D, Ruzicka T, Kolb-Bachofen V. Nitric oxide in human skin: current status and future prospects. *J Invest Dermatol* 1998;**110**:1–7.
21. Weller R, Pattullo S, Smith L, Golden M, Ormerod A, Benjamin N. Nitric oxide is generated on the skin surface by reduction of sweat nitrate. *J Invest Dermatol* 1996;**107**:327–331.
22. Whitlock DR, Feelisch M. Soil bacteria, nitrite, and the skin. In: Rook GAW (ed.), *The Hygiene Hypothesis and Darwinian Medicine*. Basel: Birkhaeuser Publishing; 2009. p103–115.
23. Mowbray M, McLintock S, Weerakoon R, Lomatschinsky N, Jones S, Rossi AG, Weller RB. Enzyme-independent NO stores in human skin: quantification and influence of UV radiation. *J Invest Dermatol* 2009;**129**
24. Bryan NS, Fernandez BO, Bauer SM, Garcia-Saura MF, Milsom AB, Rassaf T, Maloney RE, Bharti A, Rodriguez J, Feelisch M. Nitrite is a signaling molecule and regulator of gene expression in mammalian tissues. *Nat Chem Biol* 2005;**1**:290–297.

25. Duranski MR, Greer JJ, Dejam A, Jaganmohan S, Hogg N, Langston W, Patel RP, Yet SF, Wang X, Kevil CG, Gladwin MT, Lefer DJ. Cytoprotective effects of nitrite during in vivo ischemia-reperfusion of the heart and liver. *J Clin Invest* 2005;**115**: 1232–1240.
26. Lundberg JO, Govoni M. Inorganic nitrate is a possible source for systemic generation of nitric oxide. *Free Radic Biol Med* 2004;**37**:395–400.
27. Larsen FJ, Ekblom B, Sahlin K, Lundberg JO, Weitzberg E. Effects of dietary nitrate on blood pressure in healthy volunteers. *N Engl J Med* 2006;**355**:2792–2793.
28. Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, Rashid R, Miall P, Deanfield J, Benjamin N, MacAllister R, Hobbs AJ, Ahluwalia A. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. *Hypertension* 2008;**51**:784–790.
29. Jansson EA, Huang L, Malkey R, Govoni M, Nihlen C, Olsson A, Stensdotter M, Petersson J, Holm L, Weitzberg E, Lundberg JO. A mammalian functional nitrate reductase that regulates nitrite and nitric oxide homeostasis. *Nat Chem Biol* 2008;**4**:411–417.
30. Dejam A, Kleinbongard P, Rassaf T, Hamada S, Gharini P, Rodriguez J, Feelisch M, Kelm M. Thiols enhance NO formation from nitrate photolysis. *Free Radic Biol Med* 2003;**35**:1551–1559.
31. McLaren M, Kirk G, Bolton-Smith C, Belch JJ. Seasonal variation in plasma levels of endothelin-1 and nitric oxide. *Int Angiol* 2000;**19**:351–353.
32. Ringqvist A, Leppert J, Myrdal U, Ahlner J, Ringqvist I, Wennmalm A. Plasma nitric oxide metabolite in women with primary Raynaud's phenomenon and in healthy subjects. *Clin Physiol* 1997;**17**:269–277.
33. Perlman DH, Bauer SM, Ashrafian H, Bryan NS, Garcia-Saura MF, Lim CC, Fernandez BO, Infusini G, McComb ME, Costello CE, Feelisch M. Mechanistic insights into nitrite-induced cardioprotection using an integrated metabolomic/proteomic approach. *Circ Res* 2009;**104**:796–804.
34. Dezfulian C, Shiva S, Alekseyenko A, Pendyal A, Beiser DG, Munasinghe JP, Anderson SA, Chesley CF, Vanden Hoek TL, Gladwin MT. Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival via reversible inhibition of mitochondrial complex I. *Circulation* 2009;**120**:897–905.
35. Garcia-Saura MF, Fernandez BO, McAllister BP, Whitlock DR, Cruikshank WW, Feelisch M. Dermal nitrite application enhances global nitric oxide availability: new therapeutic potential for immunomodulation? *J Invest Dermatol* 2010;**130**: 608–611.
36. Lohr NL, Keszler A, Pratt P, Bienengraber M, Warltier DC, Hogg N. Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: potential role in cardioprotection. *J Mol Cell Cardiol* 2009;**47**: 256–263.