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Blue light exposure decreases systolic blood pressure, arterial stiffness, and improves endothelial function in humans

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Abstract

Aims: Previous studies have shown that ultraviolet light can lead to the release of nitric oxide from the skin and decrease blood pressure. In contrast to visible light the local application of ultraviolet light bears a cancerogenic risk. Here, we investigated whether whole body exposure to visible blue light can also decrease blood pressure and increase endothelial function in healthy subjects.

Methods: In a randomised crossover study, 14 healthy male subjects were exposed on 2 days to monochromatic blue light or blue light with a filter foil (control light) over 30 minutes. We measured blood pressure (primary endpoint), heart rate, forearm vascular resistance, forearm blood flow, endothelial function (flow-mediated dilation), pulse wave velocity and plasma nitric oxide species, nitrite and nitroso compounds (secondary endpoints) during and up to 2 hours after exposure.

Results: Blue light exposure significantly decreased systolic blood pressure and increased heart rate as compared to control. In parallel, blue light significantly increased forearm blood flow, flow-mediated dilation, circulating nitric oxide species and nitroso compounds while it decreased forearm vascular resistance and pulse wave velocity.

Conclusion: Whole body irradiation with visible blue light at real world doses improves blood pressure, endothelial function and arterial stiffness by nitric oxide released from photolabile intracutanous nitric oxide metabolites into circulating blood.

Keywords

Blue light, endothelial function, blood pressure, pulse wave velocity, forearm blood flow

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Introduction

It is accepted that beside genetic factors lifestyle plays a dominant role in cardiovascular disease (CVD) development and is an important target for prevention.[1,2] Data from the Nurses' Health Study and the Health Professional Follow Up Study show that over 60% of coronary events could be prevented by maintaining a healthy lifestyle.[3] Environmental factors, in particular sunlight exposure, clearly play a role in the development of coronary heart disease.[4] Sunlight seems to have a major influence on seasonal clustering of cardiovascular deaths. During the Medical Research Council hypertension trials it was observed that during summer

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blood pressure was consistently lower than in winter.[5] Conversely, the incidence of cardiovascular mortality and morbidity is highest in winter months and inversely correlates with sunlight exposure.[6,7] High levels of exposure to sunlight in young age are associated with a delay of CVD by up to 2.1 years in later life.[8,9] Despite these interesting findings that are consistent with the hypothesis that sunlight exposure may have protective effects in the context of cardiovascular health, the mechanisms by which light affects cardiovascular health are not well understood and need to be balanced against the negative effects of sunlight.

The electromagnetic spectrum of sunlight is predominated by infra-red and microwave (49%), followed by visible (44%; 400–700 nm wave length) and ultraviolet (UV; 7%; 10–400 nm wavelength). Most studies on the biological effects of sunlight have focused on UV light. While there is indisputable evidence that UV light is cancerogenic and is involved in the formation of melanoma and non-melanoma skin cancer[10] by causing oxidative damage to lipids, co-enzymes and DNA in the form of single-strand breaks, and protein–DNA crosslink,[11–13] and promotes skin aging, several rather positive effects are known. The best known positive example is the UV-mediated photolysis of 7-dehydrocholesterol in the skin to form vitamin D in subsequent steps. More recent research indicates that human skin contains photolabile nitric oxide (NO) derivates such as nitrosated cysteine-rich proteins (RSNOs) and nitrite, which undergo photodecomposition when irradiated with UV light.[14] This photolytically generated NO is bioactive and diffuses to deeper tissue layers, resulting in increased levels of metastable nitroso compounds (RXNOs), which then are distributed by blood throughout the circulation, and lead to a sustained decrease in blood pressure.[15,16] Furthermore, it was reported that UV irradiation reduces weight gain and symptoms of metabolic syndrome and improves exercise performance.[17,18] Mainly due to the well known negative effects of UV light, we have started to explore the biological effects of visible blue light (420–453 nm) that is not cancerogenic. Our and other researchers' preclinical results indicate that blue light induces non-enzymatic NO release from cutaneous photolabile NO derivates, mostly RSNOs similar to UV light but without inducing DNA strand breaks.[19–22] Whether or not whole-body irradiation with visible non-cancerogenic blue light mobilises enough NO from the skin to cause relevant systemic effects in the cardiovascular system is unknown. The scientific proof of the latter concept would be an important prerequisite before starting to think about the potential development of irradiation devices to modulate cardiovascular function.

Therefore, we investigated whether exposure to UV-free blue light can decrease blood pressure and increase endothelial function in healthy subjects.

Methods

Study subjects

Fourteen healthy Caucasian men, between 30 and 60 years of age were recruited at the University of Duesseldorf (August 2016 to August 2017). See Supplementary Figure 1(A) for CONSORT study flow and Supplementary Table 1 for characteristics. The study subjects were screened based on a clinical physical examination including blood pressure measurement, ECG and routine clinical test (blood lipids, C-reactive protein, full blood count, liver enzymes, haemoglobin, glucose). Inclusion criteria for participation in the study were as follows: 30–60 years of age, Caucasian, male and signed consent form. We did not include women in this proof-of-concept study to excude the influence of sex cycle-dependent variations in vascular function. Exclusion criteria were diabetes mellitus, acute inflammation, arrhythmia, active malignancy, terminal renal failure, manifest CVD (coronary artery disease, peripheral artery disease, cerebrovascular disease, heart rhythm other than sinus, arterial hypotension (systolic <100 mmHg)), active medical treatment with blood pressure-lowering medication, photodermatosis and/or photosensitivity, porphyria and/or hypersensitivity to porphyrins, congenital or acquired immunodeficiency, subjects with genetic deficiencies associated with increased sensitivity to light or increased risk of dermatological cancer (i.e. xeroderma pigmentosum, Cockayne syndome, Bloom syndrome).

Study design, endpoints and protocol

This study was designed as a two-arm randomised, controlled, crossover study. The 14 healthy male volunteers were exposed in random order to monochromatic blue light (450 nm) and control light (filter foil covering the volunteers) each on a different day separated by one week of wash-out delivered by the same irradiation device (Supplementary Figure 1).

The primary endpoint of the study was a significant change in peripheral blood pressure after 30 minutes of blue light (450 nm) irradiation compared to the control irradiation. Secondary endpoints included change in heart rate, forearm vascular resistance (FVR), forearm blood flow (FBF), flow-mediated dilation (FMD), pulse wave velocity (PWV) and concentrations of circulating NO species (NOx), nitrite, and RXNOs in plasma.

After placement of an intravenous catheter in the left cubital vein, volunteers rested over 30 minutes in a supine position on the irradiation device in a quiet air conditioned room only wearing swimming shorts and safety glasses for acclimatisation. Baseline measurements were taken immediately before exposure to 30 minures irradiation of blue light or control light and were followed over 2 hours (150 minutes timepoint). For control light exposure, the volunteers were covered during irradiation with a thin opaque foil. Blood pressure and heart rate were repeatedly measured at 5-minute intervals during and 10-minute intervals after the irradiations. FMD, FBF, FVR and PWV were measured at baseline, after irradiation and at 150 minutes. Blood draws for analysis of circulating NOx were drawn by means of an intravenous catheter at baseline (0 minutes), after irradiation (30 minutes) and in 30-minute intervals until the 150-minute timepoint. Measurements were always performed in the same order in one session. We first took blood samples from the left arm and performed FMD measurements thereafter on the right arm followed by blood pressure measurements on the right arm and, finally, performed applanation tonometry on the neck and groin. The study protocol was approved by the ethics committee of the Heinrich Heine University Duesseldorf and all volunteers gave written informed consent (Clinicaltrials.gov: NCT03226587).

Full-body blue light device

The device used in this study was the full-body blue light device (Philips Light & Health, Eindhoven, The Netherlands), a non-CE marked prototype (see Supplementary data for image of irradiation device). It was equipped with 720 LEDs emitting UV-free blue light with a peak wavelength of about 450 ± 5 nm. The irradiance level was approximately 42 mW/cm^2 at a distance between 40 and 60 cm from the skin, resulting in a fluence of 72 J/cm^2 within 30 minutes. This is comparable to irradiance levels achieved with sunlight exposure (compare 30 minutes of sunlight at midday in central Europe in winter (25 mW/cm^2) or summer (70 mW/cm^2)). The device consisted of an overhead illumination panel supported by a transportable frame. The driving and control electronics were placed in the boxes at the bottom of the frame. The illumination panel can be flipped upwards to facilitate easy access of the user to lie down on the bottom covering the boxes with electronics.

Haemodynamic monitoring

Peripheral blood pressure and heart rate were measured automatically by a sphygmomanometric cuff (Dynamap monitor) at the left upper arm in supine position. Baseline blood pressure measurements were the average of three measurments taken after 30 minutes of acclimatisation immediately before irradiation. During the 30-minute irradiation, blood pressure and heart rate were repeatedly measured in 5-minute intervals and over 2 hours after the irradiations in 10-minute intervals.

Flow-mediated vasodilation

Brachial artery FMD was measured by ultrasound (10 MHz transducer; Vivid I, GE) in combination with an automated analysis system (brachial analyser; Medical Imaging Applications, Iowa City, IO, USA) in a 21°C temperature-controlled room.[23] A forearm blood pressure cuff was placed distal to the cubital fossa and inflated to 250 mmHg for 5 minutes. Before cuff inflation, the volunteers were instructed to keep the forearm muscles relaxed during ischaemia to avoid pain, and all subjects tolerated the cuff inflation well. Diameter and Doppler flow velocity were measured at baseline and immediately after cuff deflation (0 seconds), at 20, 40, 60, and 80 seconds. FMD was the maximal brachial diameter expressed relative to baseline diameters as $(\text{diameter}_{max} - \text{diameter}_{baseline})/\text{diameter}_{baseline}$. FBF was calculated by multiplying the cross-sectional area (π*diastolic radius^2) of the brachial artery at diastole during baseline readings for FMD measurements with mean angle corrected blood flow velocity and expressed as ml/minute. The Doppler angle and measurement site was kept constant during the course of each study day in each individual. This was accomplished by marking the probe position on the arm, defining anatomical landmarks and adjustment of the ultrasound image visually before and during each measurement to align with the pre-set Doppler sample site and angle settings. See Supplementary methods for the reproducibility of FMD. FVR was calculated as mean arterial pressure (diastolic blood pressure (DBP) + ⅓ * (systolic blood pressure (SBP) − DBP)) devided by FBF.

Pulse wave velocity

PWV was determined from tonometry measurements taken at the carotid and femoral artery using the SphygmoCor system.

Quantification of NOx, nitrite, and RXNOs by chemiluminescence detection

The concentrations of total NOx (nitrite, nitrate and RXNOs), nitrite and RXNOs in plasma samples were quantified using gas-phase chemiluminescence. See Supplementary methods for details.

Statistical methods

The characteristics of the study population are expressed as mean values (standard deviation; SD) (Supplementary Table 1). The primary comparison between treatment arms in the randomised controlled trial uses repeated measurements analysis of covariance (ANCOVA) with two intra-individual factors (intervention (blue light/control light) and timepoint (30 minute change/150 minute change)) with sequence (blue light first or control light first) as a covariate to test robustly for an effect of light source accounting for differences attributable to the ordering of the interventions in individuals. Mean values of results are presented as mean (standard error of the mean) comparing the changes after irradiation (30 minutes) and after follow-up (150 minutes) from baseline (0 minutes) between the blue light and control light arms (see Table 1) and as mean intra-individual differences between responses (change at 30 minutes and 150 minutes minus 0 minutes (baseline) with Bonferroni corrected 95% confidence intervals. Further secondary analyses of time courses of blood pressure, heart rate and NO metabolites (Figure 1(a–c) and Supplementary Figure 3) were performed similarly on changes using two-way repeated measurements analysis of variance (ANOVA), with the two intra-individual factors (intervention (blue light/control light) and timepoint (all times 0–150 minites)) and sequence (blue light first or control light first) as a covariate. P values of less than 0.05 were regarded as statistically significant. All analyses were performed using SPSS 24 (IBM Corp.) and Prism 6.

Results

Baseline characteristics of study subjects

See Supplementary Figure 2 for CONSORT study flow and Supplementary Table 1 for detailed characteristics of the 14 healthy male volunteers and baseline values of endpoint parameters at the two study visits. Besides SBP (blue light 124 (SD 12) mmHg, control light 115 (SD 10) mmHg, $P = 0.001$) all other baseline values of endpoint parameters did not significantly differ between study visits. Baseline SBP inversely correlated with the average daylight hours on the day of the study visit ($r = -0.56$, $P = 0.002$).

The average skin temperature increase during blue light irradiation was comparable to the temperature increase below the foil used for control irradiations ($\Delta T = 7 \pm 1^{\circ}C$).

Blue light irradiation significantly decreased SBP as compared to control light ($P = 0.005$, Table 1). SBP decreased immediately after the initiation of blue light exposure and remained decreased as compared to baseline throughout the 30 minure irradiation (30 minute blue light; −7.6 mmHg (95% CI −11.4 mmHg, −3.9 mmHg)). After irradiation, SBP returned to baseline and remained at baseline values throughout the observation period (150 minutes blue light; −0.5 mmHg (95% CI −4.2 mmHg, 3.2 mmHg)) which was, however, significantly lower than control light in particular in the late observation period (Figure 1(a)). During control light exposure, SBP remained unchanged (30-minute control light; 1.0 mmHg (95% CI −3.3 mmHg, 5.3 mmHg)) but started to rise gradually during the observation period, resulting in significantly higher values as compared to blue light (150-minute control light; 7.1 mmHg (95% CI 3.1 mmHg, 11.0 mmHg)). Taken together, the SBP decrease due to blue light as compared to control light was −8.6 mmHg at 30 minutes and −7.6 mmHg at 150 minutes.

DBP responses did not differ between blue and control light (Table 1). Both interventions led to a bi-phasic response with slightly decreasd DBP during irradiation and increased DBP during the observation period. Heart rate was significantly increased by blue light at 30 minures (4.4 bpm (95% CI 0.8 bpm, 7.9 bpm)) but not at 150 minutes (0 bpm (95% CI −3.9 bpm, 3.9 bpm)). Heart rate significantly increased immediately on initiation and during blue light irradiation but not during control light exposure (Figure 1(c)).

Blue light exposure decreases FVR and PWV while increasing FBF and FMD

As depicted in Figure 1(d–g) and Table 1, FVR and PWV significantly decreased at 30 minutes (FVR −0.8 mmHg/ml/min (95% CI −1.1 mmHg/ml/min, −0.6 mmHg/ml/min)); PWV −0.7 m/s (95% CI −1.9 m/s, −0.5 m/s)) after blue light exposure but not control irradiation and remained decreased until after the end of the observation period at 150 minutes (FVR −0.6 mmHg/ml/min (95% CI −0.9 mmHg/ml/min, −0.3 mmHg/ml/min)); PWV −0.8 m/s (95% CI −1.3 m/s, −0.4 m/s)). FBF and FMD were significantly increased at 30 minutes (FBF 33 ml/min (95% CI 25 ml/min, 42 ml/min); FMD 2.4% (95% CI 1.8%, 2.9%)) after blue light exposure but not control irradiation and remained elevated until the end of the observation at 150 minutes (FBF 20 ml/min (95% CI 8 ml/min, 33 ml/min); FMD 2.6% (95% CI 1.9%, 3.3%)).

Blue light-induced NO release

Blue light exposure led to a significant increase in NOx and RXNO concentrations in plasma after 30 minutes irradiation (NOx 13 μmol/l (95% CI 9 μmol/l, 16 ml/min); RXNO 3 nmol/l (95% CI 2 nmol/l, 4 nmol/l))

Table 1. Endpoint analysis.

	Blue light ($n = 14$)					Control light ($n = 14$)					*P* value		
	Baseline (mean [SEM])	30 min (mean [SEM])	150 min (mean [SEM])	Δ@30 min (mean [95% CI])	Δ@150 min (mean [95% CI])	Baseline (mean [SEM])	30 min (mean [SEM])	150 min (mean [SEM])	Δ@30 min (mean [95% CI])	Δ@150 min (mean [95% CI])	Light	Light × Sequence	Light × Timepoint
Primary endpoints													
SBP (mmHg)	124 (7)	117 (7)	124 (8)	**−7.6 (−11.4, −3.9)**	−0.5 (−4.2, 3.2)	115 (6)	116 (4)	122 (8)	1.0 (−3.3, 5.3)	**7.1 (3.1, 11.0)**	**0.005**	0.053	0.522
DBP (mmHg)	70 (5)	65 (5)	72 (6)	**−4.7 (−8.5, −0.9)**	2.3 (−1.1, 5.7)	64 (5)	62 (5)	68 (8)	1.9 (−4.4, 0.6)	3.4 (−0.2, 6.9)	0.343	0.502	0.849
Secondary endpoints													
HR (/min)	58 (5)	63 (5)	58 (5)	**4.4 (0.8, 7.9)**	0 (−3.9, 3.9)	62 (4)	60 (5)	60 (5)	−1.8 (−5.4, 1.8)	−1.3 (−4.8, 2.2)	**0.001**	**0.008**	0.167
FVR (mmHg/ml/min)	1.7 (0.4)	1.0 (0.2)	1.2 (0.2)	**−0.8 (−1.1, −0.6)**	**−0.6 (−0.9, −0.3)**	1.4 (0.2)	1.2 (0.2)	1.5 (0.2)	−0.2 (−0.4, 0.1)	0.1 (−0.1, 0.3)	**0.017**	**<0.001**	0.576
FBF (ml/min)	61 (6)	92 (7)	79 (5)	**33 (25, 42)**	**20 (8, 33)**	58 (6)	64 (8)	57 (6)	6 (−2, 14)	−1 (−8, 5)	**0.016**	0.126	0.962
FMD (%)	5.6 (1.1)	8.0 (1.2)	8.2 (1.4)	**2.4 (1.8, 2.9)**	**2.6 (1.9, 3.3)**	5.7 (1.3)	5.2 (1.2)	5.1 (1.0)	−0.5 (−1.3, 0.2)	−0.6 (−1.5, 0.2)	**0.046**	0.773	0.515
BA diameter (mm)	4.58 (0.33)	4.64 (0.34)	4.49 (0.36)	0.18 (0.02, 0.35)	0.10 (−0.09, 0,29)	4.46 (0.32)	4.64 (0.30)	4.56 (0.30)	0.06 (−0.08, 0.20)	0.09 (−0.32, 0.14)	0.475	0.789	0.323
PWV (m/s)	6.3 (0.3)	5.5 (0.3)	5.4 (0.3)	**−0.7 (−1.9, −0.5)**	**−0.8 (−1.3, −0.4)**	5.5 (0.2)	5.7 (0.2)	5.7 (0.2)	0.3 (−0.1, 0.6)	0.3 (−0.2, 0.7)	**0.048**	0.337	0.675
NOx (μmol/l)	84 (8)	97 (7)	86 (5)	**13 (9, 16)**	2 (−4, 7)	82 (7)	85 (8)	86 (7)	4 (−3, 10)	5 (−2, 11)	**0.043**	0.775	0.382
Nitrite (nmol/l)	78 (8)	88 (7)	80 (7)	10 (7, 13)	1 (−5, 6)	75 (7)	79 (8)	79 (6)	4 (−2, 10)	5 (−1, 11)	0.594	0.482	0.519
RXNO (nmol/l)	6 (1)	9 (2)	6 (1)	**3 (2, 4)**	1 (−1, 2)	6 (1)	6 (1)	6 (1)	0 (−1, 1)	0 (−1, 1)	**0.046**	0.205	0.382

Mean values (standard error (SEM)) at each time of measurement and as change from baseline,expressed as average of intra-individual changes (Δ), after blue light or control light exposure (30 minutes or 150 minutes value minus baseline); 95% confidence intervals (CIs) are Bonferroni corrected.

P values are from repeated measurements analysis of covariance (ANCOVA) with two intra-individual factors (intervention (blue light/control light) and timepoint (30-minure change/150-minute change)) with sequence (blue or control light first) as a covariate.

DBP: diastolic blood pressure; FBF: forearm blood flow; FMD: flow-mediated dilation; FVR: forearm vascular resistance; HR: heart rate; NOx: nitric oxide species; BA: brachial artery; PWV: pulse wave velocity; SBP: systolic blood pressure.

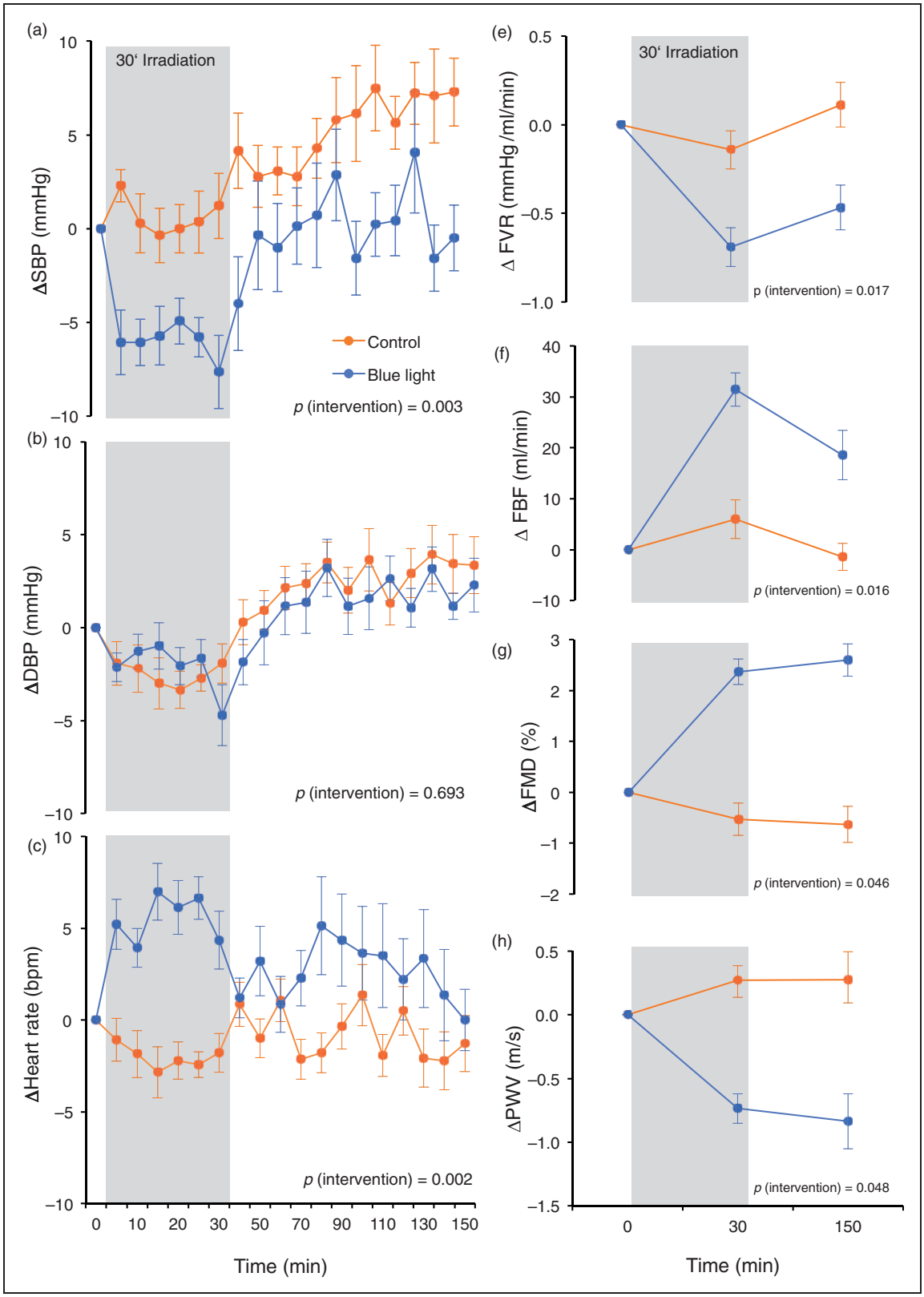

Figure 1. Effect of crossover blue light and control light irradiation on systolic and diastolic blood pressure (SBP and DBP, a and b) and heart rate (c), forearm vascular resistance (FVR, d), forearm blood flow (FBF, e), flow-mediated dilation (FMD, f) and pulse wave velocity (PWV, g). Symbols are average changes (Δ) from 0 hours baseline, error bars are SEM. *P* values refer to repeated measurements analysis of covariance with two within-subject factors (intervention and time) taking the sequence of interventions as a covariate into account.

but not at 150 minutes (Table 1). Plasma nitrite concentration exhibited high variability and no significant differences were observed between treatment. This remained statistically not significant when evaluating all data (Supplementary Figure 3). The change in SBP after 30 minutes blue light irradiation inversely correlated with changes in RXNO ($r = 0.43$, $P = 0.028$).

Discussion

Our present study demonstrates for the first time that whole-body blue light exposure at doses that are comparable to daily sunlight exposure decreases SBP, FVR and PWV while increasing heart rate, FBF, FMD, and circulating NOx and RXNO in young healthy male volunteers.

The haemodynamic effects of blue light exposure can be plausibly explained by NO released into circulating blood from photolabile intracutanous NO metabolites. We have previously shown that whole-body UV irradiation of healthy human skin significantly increases intracutaneous NO and S-nitrosothiol concentrations by decomposition of cutaneous photolabile NO derivates with the result of significantly enhanced concentrations of plasma nitroso compounds and a pronounced decrease in blood pressure.[15] More recently and keeping injurious effects of UV irradiation in mind, we have investigated the mechanism and biological relevance of blue light (420–453 nm)-induced non-enzymatic NO generation from photolabile NO derivates in human skin *in vitro* and *in vivo*.[22] We showed that blue light led to significant NO formation from S-nitrosoalbumin and also from aqueous nitrite solutions by a to-date not entirely identified Cu^{1+}-dependent mechanism, increased intradermal levels of free NO in human skin specimens, and led to the release of NO and translocation of NO from the skin surface into the underlying tissue and increased local cutaneous blood flow in healthy subjects.[22] Our current work significantly extends these previous findings by demonstrating that whole-body blue light irradiation leads to increased plasma levels of NOx together with systemic haemodynamic effects. Taken together, our data suggest that whole-body blue light irradiation can release NO from photolabile NOx in the skin into the circulating blood where they mediate clinically relevant haemodynamic effects including lowering of SBP potentially by decreasing large artery stiffness and resistance artery dilation as indicated by decreased FVR.

The pattern of haemodynamic responses to blue light exposure resemble what would be expected from increases in circulating NOx or circulating NO stores (RXNOs),[24] and are clinically relevant with regard to the magnitude of effects. While the volunteers in the present study were healthy subjects, the recent discussion on lower cut-off blood pressure values to diagnose arterial hypertension in the American Heart Association guideline illustrates that even in healthy subjects blood pressure lowering may have protective cardiovascular effects. Of note, blood pressure is strongly and directly related to cardiovascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mmHg throughout middle and old age.[25] For instance, the Systolic Blood Pressure Intervention Trial (SPRINT) recently demonstrated that targetting SBP of less than 120 mmHg, as compared to the standard goal of less than 140 mmHg, resulted in lower rates of fatal and non-fatal major cardiovascular events and death from any cause.[26] Importantly, the risk reduction appears to be rather due to the decrease in blood pressure *per se* and there seems to be little or no difference between commonly used blood pressure-lowering medications for the primary prevention of CVD.[27] The effect size in our current study is comparable to that seen with UV light exposure previously[15,22] and comparable or even higher than the blood pressure-lowering effect sizes observed by typical blood pressure-lowering medications including angiotensin-converting enzyme inhibitors (−5 mmHg), angiotensin receptor blockers (−2 mmHg), or calcium antagonists (−8 mmHg)[28] and the Mediterranean diet (−2 mmHg).[29] However, while intensive pharmacological blood pressure lowering can decrease cardiovascular risk, SPRINT also indicated that intensive pharmacological blood pressure lowering goes along with significantly more serious adverse outcomes, including kidney failure that may be in part due to the medication.[26]

In parallel with SBP lowering by blue light in our current study, we observed a significant increase in endothelial function (FMD increase 2.3–1.9%). Meta-analyses suggest that a change in FMD by 1% may reflect a decrease in cardiovascular risk by approximately 8–13%[30] indicating a potentially clinically relevant effect of our current study. These comparisons and assumptions related to long-term prognostic relevance, however, are based on the assumption that blue light exposure would be repeated regularly and effects would be sustained over longer time frames and no tachyphylaxis would occur. Taken together, the haemodynamic effects of blue light exposure may be clinically relevant even in healthy human subjects.

When assessing the present results in light of potential future applications such as wearable blue light sources, this approach offers a quick option to modulate SBP. In particular in the elderly population isolated SBP is a common feature that is not easily treated with fixed doses of drugs given chronically. This is due to the fact that the blood pressure may not be constantly elevated, but rather present with very high peaks due to,

for example, short phases of stress in face of stiff arteries. A device with a feedback system detecting such blood pressure peaks coupled with a wearable blue light source may be an interesting approach towards personalised and on-demand antihypertension therapy in elderly subjects with isolated systolic hypertension.

Limitations

The major limitation of our present study lies in the fact that no blinding could be performed as the control light exposure required the application of a filter foil. While we cannot fully explain haemodynamic effects in the control group, i.e. increase in SBP, potential explanations are stress due to 3-hour-long supine position and filter foil application during control irradiation. However, the heart rate in the control group remained stable and the skin temperature during blue light and control light exposure did not significantly differ. Furthermore, the cardiovascular preventive potential of blue light exposure needs to be evaluated in a wider and representative segment of the general population of healthy men and women, patients at increased cardiovascular risk in particular older people with arterial hypertension, and over longer time frames. This would require the development and use of wearable cold light sources.

Conclusion

Whole-body irradiation with visible blue light at doses that are comparable to doses achievable on a sunny day decreases blood pressure and arterial stiffness while improving endothelial function by NO released into circulating blood from photolabile intracutanous NO metabolites (see Supplementary Figure 1 for summarising illustration). These findings highlight the impact of environmental factors on circulatory function and, in contrast to cancerogenic UV light, encourage the development of devices for intermittent blue light application to improve vascular function as a supportive strategy to pharmaceutical approaches.

Author contribution

CH, MB, JL and CS contributed to the conception or design of the work. MS, MG, RS, MB, JL, CH, SSS, and CS contributed to the acquisition, analysis, or interpretation of data for the work. CH, JL, CS, and MS drafted the manuscript. MK, MB, JL, MG, SSS, and CS critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JL and MB are employed by Philips.

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