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# Dental resin curing blue light induces vasoconstriction through release of hydrogen peroxide

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A B S T R A C T

Dental resin curing blue light (BL) is frequently used during treatments in dental clinics. However, little is known about the influence of BL irradiation on pulpal blood vessels. The aim of the present study was to investigate the mechanism of effect of BL irradiation on vascular tone. Rat aorta (RA) rings were irradiated with a BL source in organ baths, and the responses were recorded isometrically. Effect of BL irradiation on phenylephrine (PE) -precontraction and acetylcholine (ACh) -induced relaxation after PE -precontraction were obtained and compared in BL -irradiated and control RA rings. Effect of 20 min preincubation with catalase (enzyme that breaks down hydrogene peroxide, 1200 u/ml) on PE -precontraced and BL-irradiated rings was also evaluated. Total oxidative stress (TOS) and total antioxidant capacity (TAC) in BL-irradiated and control RA preparations were measured with special assay kits and spectrophotometry. BL slightly decreased ACh -induced endothelium -dependent relaxations in PE (1 μM) -precontracted RA rings ($n = 6$, $p > 0.05$ vs. control). BL induced marked contraction 23.88 + 3.10% of PE (maximum contraction) in isolated RA ring segments precontracted with PE ($p < 0.05$ vs. control). The contractile effect of BL was inhibited by 1200 u/ml catalase ($n = 6$, $p < 0.05$ vs. control). BL irradiation increased the level of TOS in RA rings ($n = 6$, $p < 0.05$ vs. control). TAC levels were similar in BL-irradiated and control preparations. These results suggest that BL induces contraction in RA, and the mechanism of this effect may to be through release of hydrogen peroxide.

## 1. Introduction

Currently, blue light (BL) is widely used during treatments in dental clinics to photocure light sensitive restorative materials, pit and fissure sealants, bonding agents, adhesives as well as resin composites. Additionally, BL irradiation for over 10 min has been used as an in-office dental bleaching method. Several studies indicate that BL may cause cell disfunction through the action of reactive oxygen species (ROS) on mitochondrial DNA [1–5]. As all dental curing lights, BL can also cause ocular damage [6]. In addition, the heat from a powerful curing light can cause gingival or soft tissue burns. Therefore, it is important to consider its effects on oral tisues and dental pulp.

Dental pulp is rich in blood vessels and nerve fibers. Since the pulp is a close system surrounded by hard tissue such as dentin, vasodilatation in the pulp may increase the pressure in the dental pulp cavity and induce acut pain of the teeth [7]. Previously, it was reported that UV irradiation light induced photo relaxation in isolated rat aorta (RA) through expression and activation of nitric oxide syntase [8]. Likewise, Ankri et al. [9] reported that visible light illumination increased nitric oxide (NO) concentration in adult bovine aortic endothelial cells. Additionally Li et al. [10] found that peroxynitrite, the product of superoxide and NO, triggered relaxation of canine cerebral arteries through elevation of cyclic guanosine monophosphate. A previous study reported that BL might cause vasoconstriction in the blood vessels via ROS generation [11]. Hence, the exact mechanism of vascular effects of dental resin curing BL is not clear. On the other hand, the behavior of pulp microvasculature in response to various known vasoactive agents is not significantly different from RA [12]. Thereupon, we designed the present study to directly investigate the vascular effects of dental resin curing BL and its possible mechanism of action on isolated RA.

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## 2. Materials and Methods

### 2.1. Animal and Vessel Preperation

Prior approval for this experiment was obtained from the Animal Experimentation Ethics Committee at Gulhane Faculty of Medicine. Six-month-old female Wistar Albino rats were housed in a light-controlled room with a 12-h light/dark cycle under fixed temperature (22 ± 3 °C) conditions with food and water available ad libitum. The rats were used in compliance with the principle of Helsinki of the World Medical Association, and Animals of the Guide for the Care and Use of Laboratuary Animals of the Institue for Laboratuary Animal Research of the National (1996). Thoracic aortas were taken from rats under anesthesia with 100 mg/kg ketamine (Ketalar® Parke Davis, Eczacıbası, Istanbul, Turkey) and 10 mg/kg Xylazine (Rompun®; Bayer AG, Leverkusen, Germany), and the preparations were quickly dissected out and cleaned of adhering fat and connective tissues.

### 2.2. Isolated Organ Bath Experiments

Four millimeter-long aortic ring segments are cut mounted in isolated tissue baths containing oxygenated Krebs-Henseleit solution (composition in mmol/l: NaCl, 118; KCI, 4.7; $CaCl_2$, 2.5; $MgSO_4.7H_2O$, 1.2; $K_2HPO_4$, 1.2; $NaHCO_3$, 25, and D-glucose, 10), which was stabilized at 37 °C with a thermostatic circulator. Isometric tension measurements were recorded by a force-displacement transducer (model FT03; Grass Instruments, Astro-Med Inc., West Warwick, RI, USA), amplified with a strain gauge amplifier (model P122; Grass Instruments), and analyzed by a using data-acquisition and analysis software (Polyview, version 2.0; Grass Instruments). The aortic ring segments were equilibrated under final resting force of 2 g for 90 min. Then, all arterial rings were challenged with KCI (68 mM) in order to test the viability. In all experimets, after KCl-induced contraction reached to plateau, the tissues were washed every 10 min during an additional 30 min of equilibration period. In some experiments, the rings were irradiated for 5 min at a distance 10 mm with BL source (Model D-2000, Apoza, New Taipei City, Taiwan) which provided BL (400–520 nm, 1200 mV/cm$^2$). The tip of BL source was immersed in to isolated organ bath (30 ml) containing Krebs-Henseleit solution (Fig. 1). We first performed some preliminary experiments to observe effects of BL on basal vascular tone of rat aorta rings (n = 6).

In the first set of experiments, phenylephrine (vasoconstrictor selective $\alpha_1$-adrenergic receptor agonist, PE, 1 nm–10 μM) concentration -response curve were constructed in 4 preparations to decide on the concentration to achieve submaximal precontraction, and 1 μM of PE concentration was selected. Then, concentration -response curve to acetylcholine (endothelium dependent vasodilator muscarinic agonist, ACh, 1 nM–1 μM) after precontraction with phenylephrine (PE, 1 μM) were obtained in control (n = 6) or BL-irradiated (n = 6) rat aorta rings. In these experiments, BL-irradiation was performed simultaneosly with PE (1 μM) precontraction.

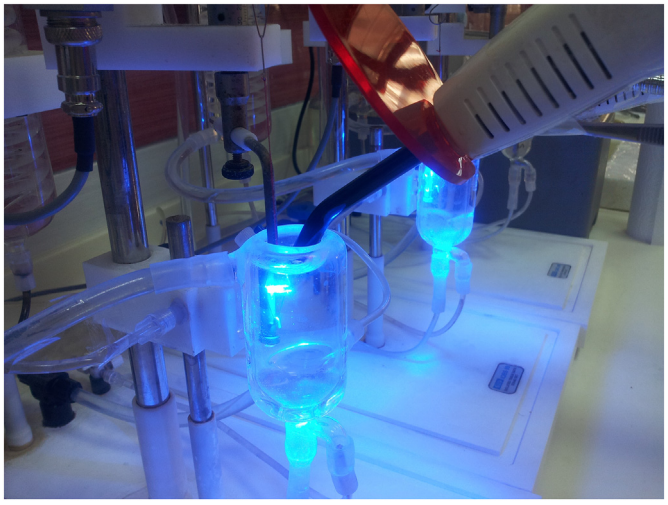

**Fig. 1.** Blue light irradiation of rat aorta rings in isolated organ bath. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the second set of experiments, after the equilibration, effect of preincubation with 1200 u/ml catalase (enzyme that breaks down hydrogene peroxide ($H_2O_2$), lyophilized powder, from bovine liver; Sigma, St. Louis MO, USA) for 20 min on PE -precontracted BL-irradiated rat aorta rings were evaluated. In these experiments, BL-irradiation was performed after PE (1 μM) precontraction reached to plateau (approximately after 5 min).

### 2.3. Tissue TOS and TAC Determination

In these experiments, total oxidative stress (TOS) and total antioxidant capacity (TAC) in BL-irradiated (n = 6) and control (n = 6) rat aorta preparations were measured with assay kits and spectrophotometry as stated below.

Rat aortic tissue samples were stored at −80 °C for the measurement of TOS and TAC until needed. For determination of TOS and TAC Rel Assay Diagnostics kits (Gaziantep, Turkey) were used. The tissues were mixed with homogenization buffer (140 mmol KCL) (1:9 w/w) then homogenized. After centrifuged 5 min at 3000 rpm, the supernatants were collected and used as samples.

Serum TOS was measured using Erel's TOS method [13] which is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species in the acidic medium. Ferric ion was measured by xylenol orange. 35 μl sample and 35 μl SSS (Standard Stabilized Solution) (20 μmol/l $H_2O_2$) were loaded on microplate wells and then 225 μl R1 ($H_2SO_4$; 25 mM, pH: 1.75) was added. Plate was shaken gently for 30 s and the absorbance was measured at 595 nm by spectrophotometer and recorded as A1. After adding rapidly 11 μl R2 (Substrate solution), $H_2SO_4$ (25 mM, pH: 1.75), Ferrous ion (5 mM), O-Dianisidine (10 mM) to the wells, the microplate was kept in room temperature for 10 min. Then the second absorbance was measured as A2. Calculation of TOS was done according the formula below:

$$\Delta Abs = A2 - A1$$

$$TOS\ (\mu mol/L) = (\Delta Abssample)/\Delta Absstandard) \times SSS\ Concentration$$

TAC was measured colorimetrically using the Total Antioxidant Status kit (REL Assay Diagnostics) [14]. 5 μl deionized water, 5 μl calibration standard reagent and 5 μl sample were loaded on microplate wells and then 225 μl R1 (Acetate Buffer (0.4 mol/l, pH: 5.8) was added. Plate was shaken gently for 30 s and the absorbance was measured at 660 nm by spectrophotometer and recorded as A1. After adding rapidly 20 μl R2 (prochromogen solution, 0.4 mol/l, pH:3.6; acetate buffer and ABTS 30 mmol/l) to the wells, the microplate was kept in room temparature for 10 min. Then the second absorbance was measured as A2. Calculation of TAC was done according the formula below:

$$\Delta Abs = A2 - A1$$

$$TAC\ (mmol/L) = (\Delta AbsH2O - \Delta Abssample)/(\Delta AbsH2O - \Delta Absstandard)$$

### 2.4. Statistical Analysis

The vasoconstrictor responses to BL were expressed as percentage of the maximum response of that tissue to PE (1 μM). Results were expressed as the mean + S.E.M. for n separate experiments and comparisons were made by paired or unpaired *t*-test. A probability of 0.05 or less was considered significant. *n* indicates the number of rat aorta rings.

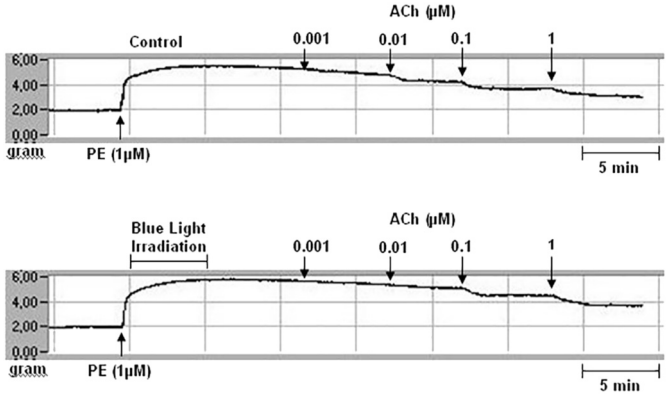


**Fig. 2.** Original tracings showing slight inhibitor effect of bluelight (BL) on acethycholine (ACh, 1 nM-1 μM) -induced relaxation of pheylephrine (PE, 1 μM) -precontracted rat aorta rings.

## 3. Results

### 3.1. Isolated Organ Bath Experiments

BL did not significantly influence basal tone in RA rings in our preliminary experiments ($n = 6$, $p > 0.05$, data not shown). Additionally, BL slightly but not significantly decreased ACh (1 nM–1 μM) -induced endothelium -dependent relaxations in PE (1 μM) -precontracted RA rings ($n = 6$, $p > 0.05$, Fig. 2).

PE (1 μM) induced marked and stable contractions in rat aorta preparations. BL induced additional contraction in isolated RA ring segments precontracted with PE (1 μM) (Fig. 3). The contractile effect of BL was significantly inhibited by 1200 u/ml catalase ($n = 6$, $p < 0.05$, Fig. 4).

### 3.2. TOS and TAC Measurements

TOS level in control group ($n = 6$) was 8.35 ± 0.45 μmol/l. However, TOS level in BL-irradiated aortas (n = 6) was significantly higher (10.45 ± 0.43 μmol/l, $p < 0.05$ versus control group) (Fig. 5). On the other hand, TAC level did not differ between BL-irradiated and control preparations (0.66 ± 0.15 mmol/l and 0.63 ± 0.11 mmol/l respectively, n = 6, $p > 0.05$) (Fig. 6).

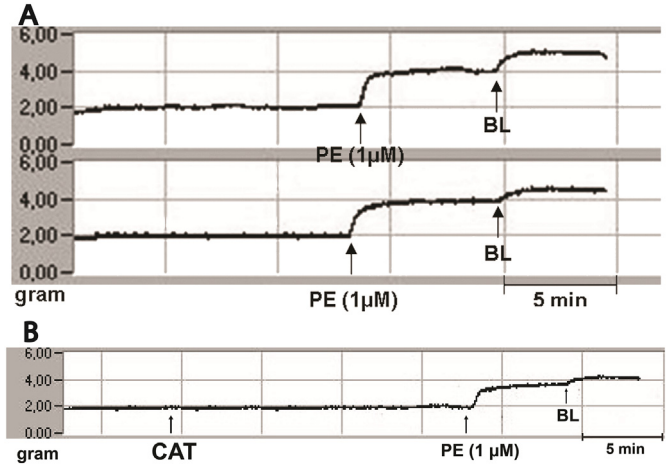


**Fig. 3.** A: Original tracings showing additional vasoconstrictor effect of bluelight (BL) on pheylephrine (PE, 1 μM) -induced tone of rat aorta rings. B: Inhibition of BL -induced contraction by catalase (CAT, 1200 u/ml).

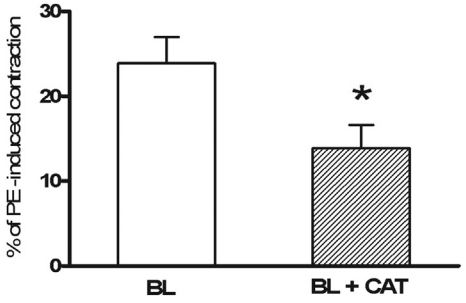


**Fig. 4.** Effect of bluelight (BL) irradiation on phenyhlephrine (PE) -induced tone of rat aorta rings in the absence and presence of catalase (CAT, 1200 μ/ml). Values are expressed as mean + S.E.M. *$p < 0.05$ versus BL (paired *t*-test).

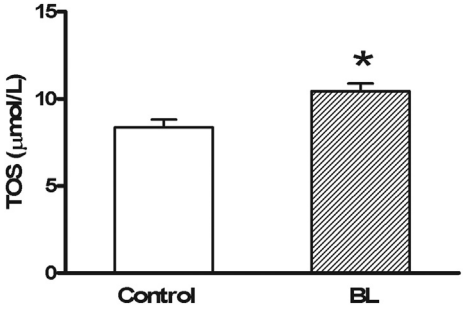


**Fig. 5.** Total oxidative stress (TOS) levels in blue light (BL) -irradiated ($n = 6$) and control (n = 6) rat aorta segments. Values are expressed as mean + S.E.M. *p < 0.05 versus control (unpaired *t*-test).

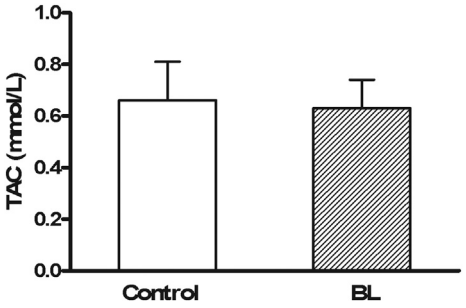


**Fig. 6.** Total antioxidant capacity (TAC) levels in bluelight (BL) -irradiated (n = 6) and control (n = 6) rat aorta segments. Values are expressed as mean + S.E.M.

## 4. Discussion

The main finding of the present study is that dental resin curing BL induces marked contraction after precontraction with PE in RA. BL -induced contraction was significantly inhibited by catalase (enzyme that breaks down $H_2O_2$), and BL irradiation increased the TOS level in RA. Consequently, our study is unique to show that $H_2O_2$ production may be involved in BL-induced vascular contraction.

Previously, Yoshida et al. demonstrated that BL irradiation in RA was inhibited by ROS scavengers [11]. However, they did not suggest an exact mechanism. In the present study, we have found that BL induces vasoconstriction in RA which is probably related to $H_2O_2$ production. Alternatively, BL may decrease degradation of $H_2O_2$ and it may induce vasoconstriction in an indirect manner. However, we have not observed an alteration in TAC, therefore, we may suggest that BL -induced $H_2O_2$ production is more likely to occur instead of BL -induced inhibition of scavenging of $H_2O_2$.

$H_2O_2$ is a powerful oxidant which is produced as a by-product of several cellular reactions. The effects of $H_2O_2$ on the vessels are

complex. Low concentrations of $H_2O_2$ (1–100 μM) may stimulate release of prostacyclin and NO from endothelial cells [15–17]. On the other hand, higher concentrations (> 100 μM) may lead to endothelial damage [18] and vascular leakeage [19]. Mian & Martin previously showed that $H_2O_2$ induced non-selective impairment of vascular smooth muscle function in rat aorta with a loss of contractile and relaxant actions [20]. They also showed that endogenous catalase might protect vascular smooth muscle function from oxidant damage by $H_2O_2$. Yang et al. also showed that $H_2O_2$, at high concentrations, could induce $Ca^{2+}$ dependent contractions in rat aorta [21] and canine cerebral arteries [22]. Separately, Shen et al. found that $H_2O_2$ might activate ATP receptors and contract rat aorta in a $Ca^{2+}$ dependent manner [23]. Gao et al. showed that $H_2O_2$ might induced endothelium-dependent contraction in rat renal artery in response to ACh stimulation [24]. Moreover, they suggested that $H_2O_2$ might be an endothelium-dependent contracting factor. In the present study, we have found that BL may induce vasoconstriction in rat aorta which is probably related to $H_2O_2$ production. Alternatively, BL may decrease degradation of $H_2O_2$ and it may induce vasoconstriction in an indirect manner. However, we have not observed an alteration in TAC, therefore, we may suggest that BL -induced $H_2O_2$ production is more likely to occur than BL -induced inhibition of scavenging of $H_2O_2$.

Interestingly, BL did not influence the basal tone, however it inhibited endothelium -dependent ACh-induced relaxation, and it induced marked contraction after precontraction with PE. The reason for this discrepancy may be related to limited production of $H_2O_2$ by BL irradiation. $H_2O_2$ could induce $Ca^{2+}$ dependent contractions at high concentrations [21–23]. In our experinetal setting, PE-precontaction occurs through $\alpha_1$-adrenergic receptor activation followed by effective $Ca^{2+}$ influx via receptor -activated $Ca^{2+}$ channels, which may potentiate $H_2O_2$ -mediated $Ca^{2+}$ influx. On the other hand, ACh induces endothelial nitric oxide release and vascular smooth muscle relaxation. The opposing vascular contraction induced by BL may partly mask this vasodilation.

It is well known that, in-office bleaching treatments, the use of curing lights are recommended to accelerate the action of bleaching gel [25]. It is believed that most light sources decompose peroxide faster (by increasing the temperature) to form free radicals which whitens teeth [25]. It was previously shown that light curing units of different intensities might generate heat emission and temperature rises [26]. Therefore, in our experimental design, it's important to know if there is a temperature rise which may alter vascular tone. In our study, there was no increase in the temperature of the physogical solution and the tissue, hence a thermostatic circulator hold the temperature stable at 37 °C during the experiment. We have shown for the first time that $H_2O_2$, which is widely used in contemporary tooth whitening (tooth bleaching) systems [25,27,28], may be produced during BL irradiation. Taken together, BL -induced production of $H_2O_2$ not only has a vasoconstrictor effect, but it may also contribute to bleaching action of BL.

The main findings of our study should be assessed though within the study limitations, i.e. we did not use pulpal vessels, however we studied with RA, which is a well-characterized tissue model for assessing the effects of various chemicals on vascular reactivity. It has been shown that the behavior of pulp microvasculature in response to various known vasoactive agents is not significantly different from this tissue as with other widely studied tissues [29]. Because the RA model can mimic smooth muscle relaxation in dental pulp vessels, previous studies utilized this model to investigate the effect of different dentine adhesives and acids on pulp microvasculature, and showed that resin -based dental materials might induce vasodilatation in rat aorta [29–34]. Therefore, the RA model provided a practical, accurate and reproducible study model investigate the possible vasoactive effects of dental materials on periapical microvascular tissue [12]. Additionally, we did not measure $H_2O_2$ concentration directly. However, we have an indirect finding indicating that $H_2O_2$ concentration was increased by BL irradiation, since BL irradiation increased the TOS level. Additionally, we have demonstrated that contractile effect of BL is significantly inhibited by 1200 u/ml catalase which is an effective concention to block $H_2O_2$ production [35]. Several sensitive methods have been developed to measure $H_2O_2$ [36]. Further future studies are needed to detect and measure $H_2O_2$ concentration before and after BL irradiation of arteries.

## 5. Conclusion

We mimicked the dental clinical conditions by irriadiating the rings for 5 min at a distance 10,0 mm with a BL source. Therefore, these results suggest the possibility that the BL irradiation of teeth in bleaching and/or preservative restoration can constrict the numerous small blood vessels in dental pulp in the oral cavity. As stated above, resin -based dental materials induce vasodilatation which might lead bleeding during dental treatments. Clinically, this opposing vasoconstrictor effect of dental resin curing BL may be relevant to decrease bleeding during dental procedures. Additionaly, a novel photocoagulation method using an irradiating blue light emitting diode was reported [37]. Interestingly, in our daily clinical practice, we have observed that BL decreases the coagulation time in gingival bleedings. Moreover, Yoshida et al. suggested that prolonged and/or repeated BL irradiation during dental procedures could cause ROS-induced oxidative stress such as ischemia-reperfusion injury on pulpal blood vessel [11]. Clinically, pre-intake of antioxidants may be helpful to avoid such detrimental effects of multiple BL irradiations.

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