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REVIEW

Cardiovascular Changes During Phototherapy in Newborns

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Summary

Phototherapy is the most effective non-invasive method of neonatal hyperbilirubinemia treatment. Application of this method can be associated with side effects including changes in the cardiovascular system. During phototherapy, the primary effects in the cardiovascular system include cutaneous vasodilation leading to skin hyperperfusion and subsequent redistribution of blood. The increased blood flow through the skin is associated with increased transepidermal water loss. Further effects include an increase in cerebral blood flow. Redistribution of blood to the cutaneous bed is compensated by hypoperfusion in the splanchnic area (mostly postprandial) and a significant reduction of the renal blood flow. Regarding closure/reopening of the ductus arteriosus, the results suggest that that phototherapy does not affect ductal patency. During phototherapy the cardiac output can be slightly reduced due to a decreased stroke volume, especially in preterm newborns. Systemic blood pressure is decreased and heart rate is elevated in both preterm and term newborns during phototherapy. The heart rate variability is slightly reduced. Symbolic dynamics analysis of the short-term HRV showed that during phototherapy the activity of the ANS regulating the heart rate is shifted towards the dominancy of the sympathetic activity. The responses in the cardiovascular system of premature/mature newborns without other pathology confirm a well physiologically functioning control of this system, even under specific conditions of phototherapy.

Key words

Newborns • Phototherapy • Regulation • Cardiovascular system

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Introduction

The hyperbilirubinemia is the most commonly occurring metabolic complication of the neonatal period. Up to 60 % of term neonates develop physiological jaundice, with a prevalence of about 80 % in preterm neonates [1]. The major mechanisms include increased erythrocyte breakdown and a transiently reduced ability of the liver to conjugate and excrete bilirubin [2,3].

In some neonates, hyperbilirubinemia reaches high values that threaten the infant with encephalopathy (Kernicterus Spectrum Disorder – KSD). In these cases, treatment aimed to decrease lowering bilirubin level is required to avoid this serious consequence – effective treatment to reduce hyperbilirubinemia includes phototherapy and exchange transfusion.

Phototherapy is currently the most effective non-invasive method of neonatal hyperbilirubinemia treatment. The main therapeutic principle of phototherapy is to accelerate the degradation and excretion of bilirubin by light. Upon exposure to light, non-polar hydrophobic unconjugated bilirubin (Z,Z-bilirubin) in the skin is converted to hydrophilic bilirubin isomers, including Z,E – bilirubin, E,Z – bilirubin, E,Z – cyclobilirubin (lumirubin) and E,E-cyclobilirubin [4]. Phototherapy

products are more water soluble and can be excreted into bile and urine, bypassing conjugation in the liver [5]. Urinary bilirubin levels can be estimated using fluorescence assay after reverse photoisomerisation of lumirubin [6].

The transformation of bilirubin to lumirubin is thought to be primarily responsible for the phototherapeutic effect [7]. In addition to those effects, compared to bilirubin, lumirubin was found to be much less toxic in cell cultures including hepatic, fibroblast as well as neural cells [8].

The effectiveness of phototherapy depends on the wavelength of the light, the irradiance intensity, the distance between the source of light and the child's body surface, the size of the exposed body surface, as well as the causes and severity of hyperbilirubinemia [9,10].

The most effective wavelength is 450-460 nm (corresponding to a blue light – typically having a wavelength of 425-475 nm). Light with a wavelength range of 400 to 520 nm and peaked at 450±20 nm is recommended (Fig. 1). Currently used devices for phototherapy use a light with a peak wavelength near 460 nm which is based on the absorption maximum of bilirubin bound to albumin *in vitro* [11].

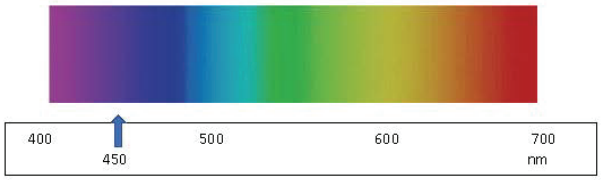

Fig. 1. The visible light spectrum. Wavelengths in nanometers (nm).

Irradiance is usually 6-12 μW/cm^2/nm in conventional phototherapy, and ≥30 μW/cm^2/nm in intensive phototherapy [12,13]. During phototherapy, as much of the body surface as possible should be exposed to light.

Commercially available phototherapy systems include fluorescent tubes, halogen lamps, light-emitting diodes (LEDs) and fibrooptic pads [12]. Today, LEDs are preferred in most of the neonatal units. Since diodes generate only a small amount of heat, the distance from the light source to the child can be significantly reduced [10,14].

The child's position is supination and alternates with the pronation position, at least once every three hours. The duration of phototherapy is up to several tens of hours depending on the condition severity and the phototherapy effectiveness. The child should be in a well-maintained thermoneutral environment, with regular feeding and, if necessary, with increased fluid supply due to increased transepidermal loss of water (TELW) (Fig. 2).

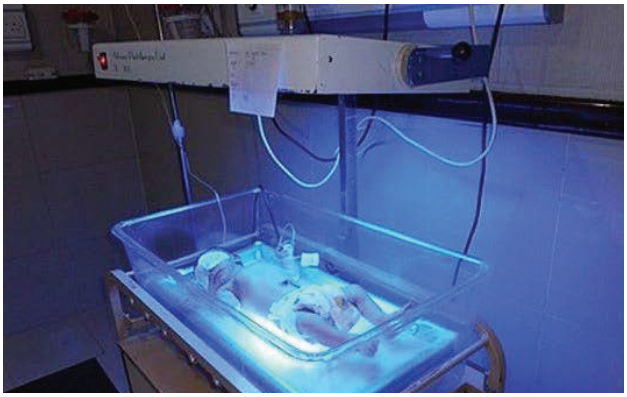

Fig. 2. Phototherapy of jaundiced newborn. From: https://www.emedicinehealth.com/newborn_jaundice/article_em.htm

The effect of phototherapy on the cardiovascular system

Phototherapy is associated with both short- and long- term side effects. It is generally accepted that the side effects are not severe and are well tolerated [15]. Nevertheless, it is important to better understand these side effects. Moreover, as an additional benefit, the study of these complex changes can provide more detailed information on the physiological control mechanisms development in preterm and full-term neonates.

Short-term side effects of phototherapy in newborns with jaundice also include changes in the functional parameters of the cardiovascular system. The study of the circulatory changes and their mechanisms may reveal specific changes on the cardiovascular regulation under the artificial conditions of phototherapy.

Cutaneous vasodilation and redistribution of blood flow is the the primary change in the cardiovascular system during phototherapy.

Redistribution of blood flow

Phototherapy of neonates with hyperbilirubinemia causes vasodilatation in the *skin vessels*, resulting in 40-70 % increase in diameter of the skin vessels and 2.5-fold increase in the cutaneous blood flow. The relative increase in blood flow through the skin tends to be higher in preterm compared to full-term

neonates [16-20]. Vasodilation in the skin may have a beneficial effect supporting the phototherapeutic effect because it increases the bilirubin content in the irradiated skin, as pointed out by Hodr [21] as early as 1979. Phototherapy increases skin blood flow by a mechanism known as photorelaxation, but the effect of heat, especially during intensive phototherapy, or other mechanisms may also be involved.

There is a relationship between cutaneous blood flow and transepidermal water loss (TEWL) that is particularly pronounced in preterm infants. Maayan-Metzger *et al.* [22] found that the average TEWL during phototherapy was increased by ~26 %. Dirk *et al.* [23] studied whether phototherapy itself, without significant heat stress, would affect water loss through the body surface. The results showed that TEWL increased by ~20 % during phototherapy, despite constant skin temperature, ambient temperature and relative humidity. This finding is relevant not only to confirm cutaneous vasodilation, but also to justify extra fluid intake during phototherapy.

The increase in the skin blood flow has responses in various regional circulations of the body. Benders [24] studied changes in blood flow through *the cerebral circulation* in premature newborns (gestational age less than 32 weeks). Using Doppler ultrasound method they found that the mean cerebral blood flow velocity increased significantly after the beginning of phototherapy. The change returned to baseline values after discontinuation of phototherapy in spontaneously breathing newborns.

Dani and coworkers [25] performed cerebral Doppler ultrasound examination in premature newborns before phototherapy, 6-12 h, 24-36 h after the start of phototherapy and 6-12 h after phototherapy termination. They found that peak systolic blood flow velocity and mean blood flow velocity increased during phototherapy and the increase ceased when phototherapy was stopped. The enddiastolic blood flow velocity and resistance index were unchanged. Conventional phototherapy as well as fiber optic phototherapy had similar effects on cerebral haemodynamics. Both were associated with an increase in cerebral blood flow velocity.

A similar protocol was used by Bertini *et al.* [26], but they compared the effects of the conventional and LED phototherapy on transepidermal water loss (TEWL) and cerebral hemodynamics. Using the LED system, TEWL through the skin remained unchanged (in contrast to the work of Dirk *et al.* [23]) as did cerebral blood flow velocity (CBFV). Conventional phototherapy was associated with a significant increase of TEWL as well as the peak systolic and mean cerebral blood flow velocities in preterm infants.

The above results indicate that cerebral blood flow of neonates does not decrease generally during phototherapy, but it increases mostly when conventional phototherapy is used.

Another important regional circulation that could be affected by blood redistribution during phototherapy is *the coronary circulation*. Borenstein-Levin *et al.* [27] studied the potential changes hypothesizing that due to the so-called "steal phenomenon" by preferring skin perfusion, the blood flow velocity in this regional circulation would decrease. Flow velocity [peak diastolic velocity (Vd)] and flow measures [diastolic time velocity integral (TVId) and flow index (FI)] in the left main (LM) and left anterior descending (LAD) coronary arteries were studied with Doppler ultrasound before, during and after phototherapy in full-term jaundiced neonates and in controls. The study showed no significant decrease in measures of velocity and flow in coronary circulation during phototherapy. They conclude that no clinically significant alteration in coronary arterial flow occurs during phototherapy in healthy term neonates.

Important changes may occur in *the mesenteric circulation*, because this region is significantly involved in blood redistribution even in premature newborns [28]. The superior mesenteric arterial blood flow (maximum, minimum) velocity and resistive index (RI) were measured in the study of Kadalraja *et al.* [29] by pulsed wave Doppler ultrasound in preterm newborns before and 8-12 h after the start of conventional phototherapy. The maximum velocity and RI before and after the phototherapy initiation were not significantly changed but minimum velocity after phototherapy was significantly increased. Increased superior mesenteric artery enddiastolic blood flow velocity may indicate photorelaxation of the mesenteric vascular smooth muscle due to phototherapy.

On the other hand, Yao *et al*. [30] found that phototherapy reduces the postprandial increase in blood flow in the mesenteric circulation in both preterm and term infants. Similar results were found by Pezzati *et al*. [31], who evaluated changes in blood flow in the mesenteric circulation using conventional and fibrooptic phototherapy. They observed a more prominent reduction in postprandial blood flow when the conventional phototherapy was applied.

Phototherapy of neonates with hyperbilirubinemia is also accompanied by a significant reduction in *the renal blood flow* and increase in renal vascular resistance after initiation of phototherapy lasting more than 12 h. Both blood flow velocity and vascular resistance values returned to baseline in infants without artificial lung ventilation after phototherapy [32].

There is only a limited information on hemodynamic changes in *the pulmonary circulation* during phototherapy. The effect of phototherapy, together with effects on cardiac output and brain and kidney perfusion was studied by Benders *et al.* [33] in term newborns with pulsed Doppler ultrasound. Mean blood flow velocity in the left pulmonary artery (LPA) increased significantly after 12 h exposure and returned to pre-phototherapy values after its termination.

An important question is whether phototherapy can affect closure of *the ductus arteriosus (DA).* A positive relationship between phototherapy and persistent DA was first described in premature neonates with respiratory distress syndrome [34]. Benders *et al.* [33] studied the closure/reopening of the ductus arteriosus in preterm neonates who had closed DA prior to phototherapy. During phototherapy, reopening of the ductus arteriosus occurred in more than half of the infants.

It was hypothesized that light could penetrate the thin chest wall, especially in extremely preterm infants, and cause relaxation of the smooth muscle of the large vessels through direct activation of the nitric oxide (NO) pathway, cyclic GMP, and Ca^{2+}-dependent K^{+} ion channels [14,35]. *Via* these mechanisms, phototherapy could inhibit DA closure or reopen it [33]. Therefore, it was recommended to shield the child's chest during phototherapy in the supine position with a metal foil.

On the other hand, the results of Surmeli-Onay *et al.* [36] showed that phototherapy did not affect the duct patency. Similarly, Kapoor *et al.* [37] reported that shielding the chest of preterm neonates during phototherapy does not have a significant effect on the incidence of hemodynamically relevant patent ductus arteriosus.

Other cardiovascular changes accompanying phototherapy, such as redistribution of blood flow to the periphery, reduction in arterial blood pressure, and increase in heart rate, may also influence DA closure [38]. Therefore, it has not been ruled out that phototherapy, especially in infants with birth weight less than 1500 g, may affect ductus arteriosus closure by mechanisms other than direct light effect [14]. Further studies are needed to find other factors potentially influencing DA closure especially in preterm neonates during phototherapy.

Changes in cardiac output (CO)

The redistribution of blood to the skin circulation may also have an impact on the pumping function of the heart. Walther *et al.* [18] found that during phototherapy there is a slight reduction in cardiac output (about 6 %) due to a reduction of the stroke volume (SV), as early as 30 min after the start of phototherapy. Similarly, Benders *et al.* [33] found that left ventricular outflow decreased after the initiation of phototherapy, but it returned to the pre-phototherapy levels within 12 h of phototherapy.

In more recent works, Firouzi *et al.* [39] found that the mean stroke volume, before and after phototherapy, was 6.99±2.17 l/m^2 and 6.55±1.84 l/m^2, respectively, and concluded that phototherapy reduces stroke volume in newborns. On the other hand, Taksande *et al.* [40] found no significant differences in echocardiographic and Doppler cardiac performance measures in newborns during phototherapy, including ejection fraction and blood flow velocity across the mitral orifice. They concluded that phototherapy in newborns has no adverse effects on either systolic or diastolic function of the left ventricle.

The results suggest possibility that a slight decrease in CO during phototherapy may occur, especially in preterm newborns. The cause of this decrease could be not only redistribution of blood and reduction of venous return, but also reduced motor activity of the infant [18]. Although the reduction in CO is small, it may further impair the peripheral tissues perfusion (e.g. in the splanchnic and renal circulation) in the smallest premature infants or in pathological newborns.

Changes in blood pressure

Blood redistribution, changes in peripheral vascular resistance, and cardiac output could be expressed in systemic blood pressure changes. Javorka and Zavarská [41] studied the effect of phototherapy on blood pressure and other cardiorespiratory parameters in preterm newborns. They used a new patented device for measuring blood pressure in newborns based on the Doppler effect [42]. This method was able to non-invasively measure blood pressure and, after completing

the ultrasound tonometer with an electromanometer and a recorder, to register intermittently the blood pressure in newborns on the brachial artery. During several hours lasting phototherapy, after 4 h, both systolic and mean blood pressures decreased and heart rate increased. After 8 h of the phototherapy duration, blood pressure tended to return to baseline values.

Similarly, Ergenekon *et al.* [43], Turan *et al.* [44] and Abu Faddan *et al.* [45] in both preterm and full-term newborns found that blood pressure decreases during phototherapy. Nandrážiová *et al.* [46] in preterm newborns found a decrease in systolic, diastolic and mean blood pressure after the 1st hour of phototherapy. This decrease was more prominent after the 2nd hour of phototherapy. There were no cardiorespiratory changes in the control group with the same characteristics (gestational age, postnatal age, etc.) as the group with phototherapy but without the irradiation.

The decrease of the systemic blood pressure could be a result of a massive cutaneous vasodilation, accumulation of blood on periphery and decreases in venous return as well as cardiac output. Compensatory physiological reactions like vasoconstriction mainly in the renal circulation help to maintain blood pressure at physiological levels, especially in mature newborns. Excessive vasodilation can lead to clinically significant hypotension in haemodynamically unstable neonates, e.g. in severe immaturity, sepsis, or infection. Therefore, in such cases, it is also advisable to monitor blood pressure during phototherapy.

Changes in heart rate and in heart rate variability

Javorka and Zavarská [41] found that heart rate increased in the first hour of phototherapy and after 4 h it was increased from 134.2±4.0 to 139.7±4.5 min^{-1}. After 8 h of phototherapy, when the blood pressure had already tendency to return to the baseline values, both heart rate and skin temperature increased further. The increased heart rate during this period may have been promoted by a body temperature increase, but also an effort to maintain cardiac output with reduced venous return and stroke volume.

Similar changes were observed by other authors finding a significant increase in heart rate during phototherapy. Nandrážiová *et al.* [46] confirmed a rise in heart rate during a two-hour lasting interval of phototherapy in hyperbilirubinemic newborns, in contrast to control infants. The study by different measurements methods showed an almost identical decrease in systemic blood pressure during the first hours of phototherapy and a mirror-like rise in heart rate.

The significant increase in heart rate may be compensatory to the blood pressure fall mediated through functioning baroreflexes even in premature newborns [47,48]. We can hypothesize that not only high-pressure but also low-pressure baroreceptors of the right atrium may play a role in the heart rate increase associated with a decrease in venous return and blood pressure during phototherapy. In addition, other mechanisms including an increase in body temperature and the effect of NO on the cardiac pacemaker may be involved in the observed heart rate increase.

Heart rate variability (HRV) indicating potential cardiac autonomic control alterations during phototherapy was first studied by Weissman *et al.* [49] in preterm newborns. By the time domain and Poincaré plot analysis of HRV, they found that there is a reduction in heart rate variability during phototherapy.

Symbolic dynamics methods were used to assess short-term HRV (time series of 300 RR intervals) during phototherapy by Uhríková *et al.* [50]. They used the following parameters: NCI (normalized complexity index), NUPI (normalized unpredictability index), PC (Pattern Classification) and Time Irreversibility – Porta index (P%). Results of this study suggest a shifted autonomic balance in icteric neonates compared to the controls and its further alterations during phototherapy. Hyperbilirubinemia was associated with mildly increased parasympathetic activity and phototherapy with vagal withdrawal and/or sympathetic activation (Fig. 3).

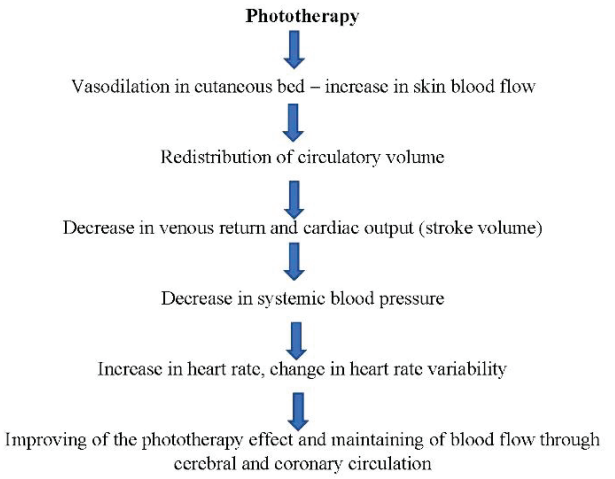

Fig. 3. Scheme of the cardiovascular changes during phototherapy.

Conclusions

Complex changes in cardiovascular system occur during phototherapy in hyperbilirubinemic newborns. The primary change in the cardiovascular system is vasodilation and increase in cutaneous blood flow. Consequential effects including an increase in cerebral blood flow, postprandial hypoperfusion in the splanchnic area and vasoconstriction in the renal circulation, a small decrease in cardiac output as well as a resulting decrease in systemic blood pressure with increased heart rate and sympathetic chronotropic activity are compensatory and adaptive responses. These changes indicate the presence of properly functioning control of the neonatal cardiovascular system, adequate for age and maturity even under the specific conditions of phototherapy.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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