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Research Paper

Effect of timing of umbilical cord clamping and birth on fetal to neonatal transition: OpenModelica-based virtual simulator-based approach

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ABSTRACT

The transition from fetal to newborn condition involves complex physiological adaptations for extrauterine life. A crucial event in this process is *the clamping of the umbilical cord*, which can be categorized as immediate or delayed. The type of clamping significantly influences the hemodynamics of the newborn. In this study, we developed a simulator based on existing cardiovascular models to better understand this practice. The simulator covers the period from late gestation to 24 h after birth and faithfully reproduces flow patterns observed in real-life situations (as evaluated by clinical specialists), considering factors such as the timing of cord clamping and the altitude of the birth location. It also reproduces blood pressure values reported in clinical data. Under similar conditions, the simulation results indicate that delayed cord clamping leads to increased oxygen concentration and improved blood volume compared to immediate cord clamping. Delayed cord clamping also had a positive impact on sustained placental respiration. Furthermore, this study provides further evidence that umbilical cord clamping should be based on physiological criteria rather than predefined time intervals.

1. Introduction

The transition of a human being from the prenatal or fetal condition to becoming a newborn is a complex process that involves the adaptation of physiological functions to the new extra-uterine environment. This transition involves several physiological processes, including the closure of fetal shunts, expansion of the lungs, elimination of placental circulation, among others [1,2]. Therefore, the umbilical cord plays a crucial role in mediating the adaptation of the newborn to extrauterine life.

1.1. Motivation for this study

The timing of *Umbilical Cord Clamping (UCC)* influences the physiology of vital organs in normal newborns, premature infants, and patients with congenital heart defects [3–7].

Generally, *UCC* has been divided into two main categories: Early Cord Clamping (*ECC*) and Delayed Cord Clamping (*DCC*). Regarding this matter, Fig. 1 offers an overview of how these categories have been defined across different studies [8–32] and medical guidelines [5,33–36]. This review is not intended to be exhaustive, but rather representative of the current perspective on *UCC* timing.

As observed in Fig. 1, the definition of *DCC* varies widely across studies. In some studies, *DCC* is defined at specific moments that are depicted as blue points in Fig. 1 (e.g., see Refs. [11,12,17] in Fig. 1). Other studies define *DCC* by fixed time intervals that are represented as blue bars in Fig. 1 (e.g., see Refs. [10,20,30]). *DCC* has been also defined as open intervals of time that are represented by blue dot-right-arrows in Fig. 1 (e.g., see Refs. [8,29,33]).

Concerning *ECC*, some studies define it as the practice of conducting *UCC* immediately following birth [11,17]. Meanwhile, other studies define *ECC* as the *UCC* taking place within a specified open or closed time interval (e.g., see Refs. [16,33,34] in Fig. 1). By venturing to combine the definitions, *UCC* may be referred to as *ECC* if conducted within the first 30 s following birth.

Fig. 1 clearly depicts a notable issue: there is no consensus on defining *ECC*, and, even more ambiguous, on how to define *DCC*. This fact has been consistently emphasized in various sources in the literature [37–45].

Until 1960, the practice of delayed cord clamping to allow for placental transfusion was prevalent and endorsed by renowned caregivers throughout the history [46]. With the advancements in modern

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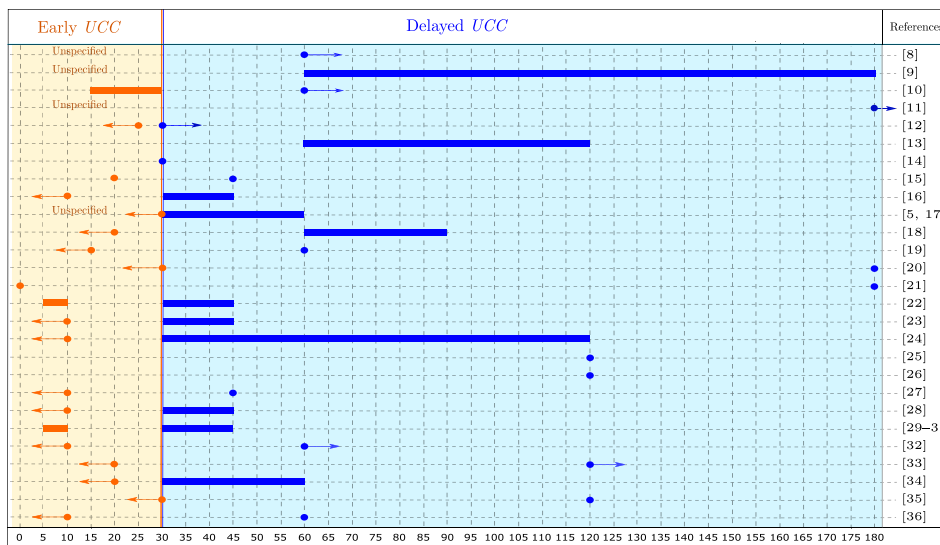


Fig. 1. An overview of the definitions for ECC and DCC.

Table 1
Contraindications for DCC in term newborns, derived from the review by Bruckner et al. [45] and the meta-analysis by Liyanage et al. [48].

Category	Contraindication for DCC
Infants contraindication	Need for immediate neonatal resuscitation, monochorionic twins, birth asphyxia secondary to hypoxic-ischemic events, shoulder dystocia, twin–twin syndrome, fetal hydrops, heart rate <60 beat per minute which is not getting faster.
Maternal contraindications	Rhesus disease, cesarean delivery under general anesthesia, massive uterine bleeding, collapse, cardiac arrest, amniotic embolism, healthy newborns from HIV-positive mothers.
Uteroplacental contraindications	Fetal hydrops, doubts about the integrity of the umbilical cord, placental detachment, cord prolapse, vasa previa, uterine rupture, amniotic embolism.

medicine, the practice of DCC was replaced by the efficiency and expedience of ECC without a proper assessment of its safety [8,47]. Recent studies tend to favor DCC as beneficial over early clamping, which tends to cause harm [4,8,45,48]. For healthy term infants (the focus of the model presented in this research), DCC increases hematocrit, blood pressure, blood volume, and iron stores, decreases anemia, and seems to result in increased myelin content and improved neurodevelopment compared with ECC [8,45]. In light of current evidence, during the last decade most guidelines have been updated to recommend performing DCC for healthy (term and preterm) infants [48], except when ECC is necessary because of neonatal, maternal or uteroplacental contraindications, as outlined in Table 1. Despite this, ECC in healthy newborns remains a widespread practice [49,50] partly due to a mindset entrenched in a fifty-year tradition [47] and, in certain instances, a lack of awareness of the latest evidence [50], among other complex reasons [47].

It goes without saying that a fundamental goal of humanity is to ensure the utmost well-being for newborns in a wise manner. Therefore, in order to bring the known potential benefits of DCC for most newborns, world-referenced health organizations such as AAP¹ [34] and ACOG² [5] recommend delaying the UCC for at least 30–60 s, whereas WHO³ for at least 60 s [33]. Other studies (and guidelines from governing bodies) suggest that the neonate only may receive the

full benefits of DCC when performed at least at 120 s [23,24,29,31] or at 180 s [8,18,19], or even longer [8,48]. These differences in expert opinions give rise to the following still incomplete set of open questions:

- (Q1) Consider a healthcare team, a midwife or a clinician preparing to perform DCC on a healthy term infant. They might opt to conservatively adhere to the AAP’s recommendation of 30 s, the WHO guideline of 60 s, or other evidence-based recommendations with DCC at 2, 3, or 5 min. Are all these recommendations relatively similar in terms of facilitating the newborn’s adaptation process?
- (Q2) Given that ECC is conducted based on long-standing practice or necessity. If the clinical scenario permits a short delay, can ECC performed immediately after birth be equated to ECC conducted 30 s post-delivery?

Given the lack of a consistent definition for DCC (and ECC), numerous studies in the literature converge to highlight the importance of determining the optimal timing for UCC [37–45,51]. As explicitly noted by Bruckner et al. [45], there are currently no studies examining different durations of DCC in healthy term infants, even though the optimal duration for cord clamping remains undetermined. This leads us to pose the last open question.

- (Q3) Should the focus of research be on determining the optimal timing for UCC?

1.2. Background

A commonly used method for evaluating UCC is through controlled clinical trials [38,39,52–56] or with animal subjects [57,58]. However, conducting these studies with neonatal patients presents significant ethical and clinical limitations. Consequently, in silico clinical trials based on mathematical models that describe physiological systems [59–63], specifically models of neonates’ physiology as presented in Refs. [64–69], offer a safe alternative in the initial stages of studying medical treatments [70]. However, it is important to clarify that the validity of this approach depends on the quality of the models used and the accuracy with which their parameters can be estimated.⁴

⁴ Traditionally, these parameters are obtained from clinical studies involving humans and physiologically “similar” mammals [57,58].

¹ American Academy of Pediatrics.

² American College of Obstetricians and Gynecologists.

³ World Health Organization.

In the context of mathematical models of neonatal physiology, Sá-Couto et al. [69] have presented a fetal hemodynamic simulator designed for educational purposes. This simulator enables the study of the transition from fetus to neonate and the effects of *UCC*. It accurately represents various physiological changes, including the increase in neonatal systemic resistance caused by *UCC*, alterations in intrathoracic pressure due to replacement of lung fluid with air in the bronchoalveolar tract, and changes in lung resistance resulting from lung expansion and closure of the ductus arteriosus. The simulation model is noteworthy for its simplicity and fidelity. However, it does not incorporate several important aspects, such as the timing of *UCC* occurrence, the cessation of placental circulation due to occlusion of the vein and umbilical arteries during *UCC*, processes related to oxygen uptake, transport, and consumption, the transition from placental to pulmonary respiratory function at birth. The model also does not account for the impact of altitude on neonatal adaptation, which is an important factor, as studied by Niemeyer [71].

In the same context, one of the most comprehensive models of the fetal-neonatal transition and the impact of immediate clamping at birth (*ECC*) and clamping when placental flow has a significant decrease (*DCC*) is presented in Yigit et al. [67]. This model incorporates several aspects, including the transfer of respiratory function from the pulmonary to the placenta, occlusion of the umbilical vein and arteries, and oxygen uptake, transport and consumption. It also distinguishes various structures such as the brain, liver, and intestines. However, despite its broad scope, this model does not account for certain relevant physiological processes, such as the occurrence of *UCC* at different time points, the altitude at which birth takes place [71], the inertial effect of blood in the ductus arteriosus [72], the inertia of blood between systemic arterial compartments [73], the variation in extrathoracic pressure, and the resistance to blood flow entering the atria.

The main objective of this study is to perform an impartial assessment of the direct impact of the moment of umbilical cord clamping on the transition of full-term newborns to extrauterine life. To achieve this, we have developed a computational model that simulates various components of the models proposed by Sá-Couto et al. [69] and Yigit et al. [67], incorporating new and relevant contributions. The computational model we propose allows replication of significant phenomena associated with umbilical cord clamping in healthy full-term newborns. To the best of our knowledge, this marks the inaugural effort to systematically evaluate cord clamping practices, introducing a computational model capable of simultaneously assessing two fundamental factors that significantly influence adaptation to extrauterine life: the *effect of the moment of clamping the umbilical cord* and the *effect of the altitude at which the birth occurs*. The simulator is based on a lumped parameter model (LPM) of the fetal cardiorespiratory system, which can accurately represent the transition from late gestation to the neonatal period, encompassing the most significant changes from fetus to neonate. The simulator was developed in MODELICA, which is a state-of-the-art object-oriented language for modeling complex systems [74].

In summary, the simulation model proposed in this study enables the representation of the following physiological processes: umbilical cord clamping at any given time or altitude, the cessation of placental circulation, and the influence of sanguine inertia. Furthermore, this model can also be utilized to simulate cardiac pathologies, as demonstrated in our previously published work [64].

This research is structured as follows: Section 2 presents the mathematical model underlying the simulator. In Section 3, the simulator results are presented under different *UCC* scenarios. Section 4 discusses the results presented in Section 3. Section 5 outlines the limitations of the proposed approach. Section 6 outlines the next stages of this study. Finally, Section 7 presents the conclusions drawn from the results of this study.

2. Methods

2.1. Description of the mathematical model of the fetus-neonate transition

Fig. 2 illustrates the overall structure of the model presented in this study, which enables the representation of hemodynamic and respiratory transitions from fetus to neonate. This study expands upon the neonatal pathology simulator that was previously introduced in Ref. [64]. The expanded model incorporates the *ductus arteriosus*, *foramen ovale* and *placental circulation*. The *ductus arteriosus* is represented by the path connecting pulmonary and intrathoracic arteries through resistance R_{13} and inertia I_1 . The *foramen ovale* is represented by the path connecting right and left atria through resistance R_{14} and valve V_5 . The *placental circulation* is represented by the path connecting intrathoracic veins and extrathoracic arteries through resistances R_{11} and R_{12} and elastance E_7 . These elements have been integrated into the model based on the fetal hemodynamic transition at birth model proposed by Sá-Couto et al. [69].

Within this model, component h_1 calculates the partial pressure of oxygen available based on the altitude above sea level. The time-varying elastance elements, denoted as E_{v1} to E_{v4} , represent the atria and ventricles (see Ref. [64] for a detailed mathematical description of these elements). Notice that the elements labeled as R_2 , R_3 , R_7 , R_{11} , R_{12} correspond to vascular resistances, which undergo changes as a result of *UCC*, whereas resistance R_{14} changes at birth. Components labeled as S_1 and S_2 correspond to pulmonary and placental respiratory functions, respectively. All the remaining components of the model – namely, elastances E_1 to E_7 , resistances R_1 , R_4 to R_6 , R_8 to R_{10} , and inertias I_1 to I_2 – have constant values. Most numerical values for the model's parameters were sourced from Refs. [69,73,75]. These studies compile a comprehensive range of sources for these parameters, including empirical measurements in both humans and animals, as well as physical considerations related to human anatomy.

This simulator has the ability to compute not only the hemodynamic variables described in [64] but also all the physiological transitions triggered by birth and the *UCC*. The most representative advancements of this model, compared to previous studies [64,66,67,69], are outlined below:

- *Uptake and supply of pulmonary* [O_2]. The model incorporates a component to represent the uptake of oxygen from the environment across the alveolar-capillary membrane.
- *Uptake and supply of placental* [O_2]. The model incorporates a component that represents the transfer of oxygen across the placental barrier.
- *Transport and consumption of gasses*. The model's components, including vascular resistances, cardiac valves, elastic compartments, and inertia, incorporate a novel set of mathematical equations describing the transport and utilization of gasses.
- *Cessation of blood flow from the placenta to the neonate after the UCC*. To model this effect, an equation for the change in vascular resistances R_{11} and R_{12} is proposed.
- *Transition from fetus to neonate at different heights above sea level*. This allows studying the effect of altitude on the neonate's oxygen saturation.

It is worth mentioning that each block in the model depicted in Fig. 2 was implemented using the MODELICA language (refer to [64] and the related references). The top layer to connect the model components was inspired by the PHYSIOLIBRARY library in its version 2.3.1 [76–78]. Specifically, this simulator consists of 47 components, amounting to 1600 lines of programming code.⁵

⁵ The complete code of the simulator can be found in the GitHub repository <https://github.com/ehsepulvedao/PatientEvoPhysio>.

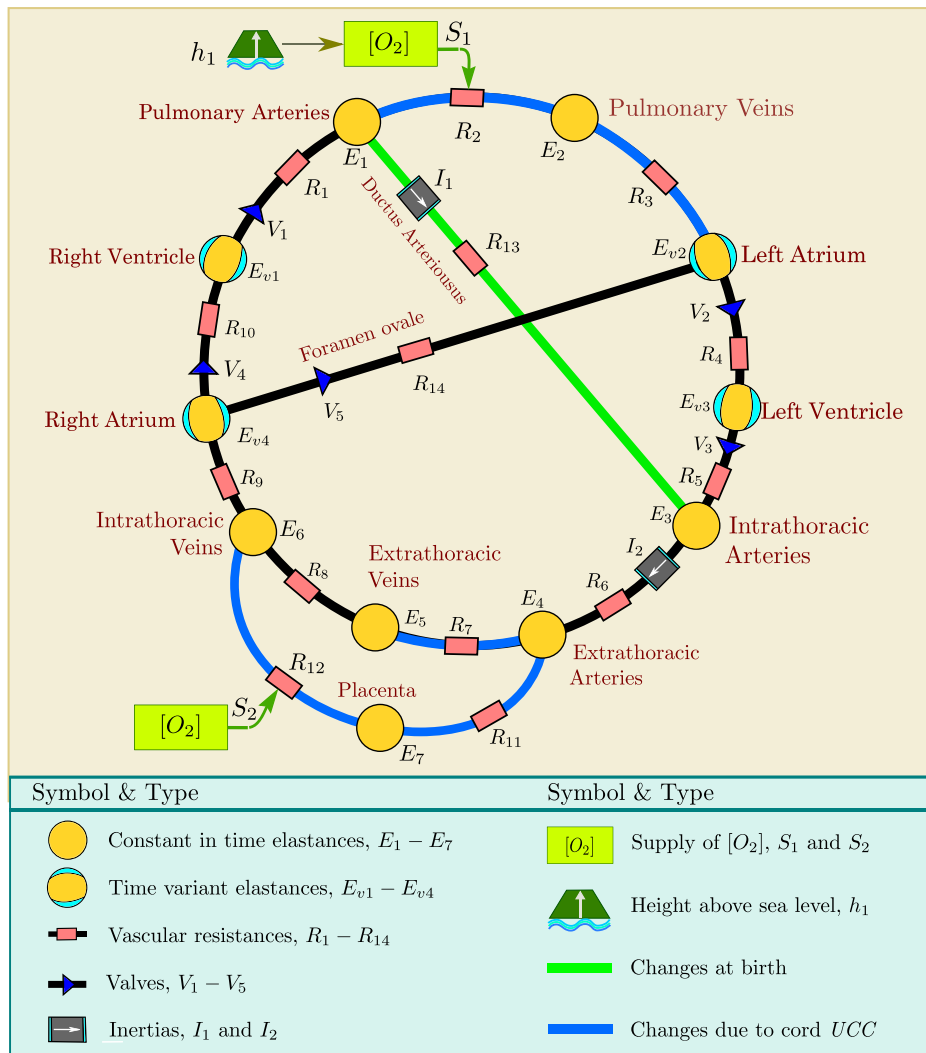


Fig. 2. Cardiovascular and respiratory model including birth and UCC.

2.2. Simulated physiological transitions

The model depicted in Fig. 2 enables the simulation of essential physiological transitions that occur in newborns during the first 24 h of extrauterine life, as elaborated in the subsequent discussion.

2.2.1. Change in intrathoracic pressure

The bronchoalveolar tract of the fetus is filled with lung fluid, leading to lung distention and an intrathoracic pressure of approximately 0 mmHg [79]. Upon birth, the lung fluid is replaced by air, initiating ventilation. This spontaneous ventilation process induces diaphragm contraction, resulting in a reduction in intrathoracic pressure around -3 mmHg [80].

2.2.2. Start of lung respiration

Both the fetal and neonatal circulatory systems supply oxygen (O_2) to the metabolizing organs and return blood containing carbon dioxide (CO_2) to the gas exchange organs for replenishing oxygen and removing CO_2 . At birth, the function of gas exchange is transferred from the placenta to the lungs. This means that the intake of oxygen by the newborn shifts from the systemic circulation to the pulmonary circulation [1].

In this model, pulmonary respiration, referred to as oxygen intake ($[O_2]_{in}$), occurs in the pulmonary peripheral vessels (represented by

component R_2 in Fig. 2). Pulmonary respiration is calculated using the following equation from Yigit et al. [67]:

$$[O_2]_{in} = r[O_2]_I - r \frac{H([O_2]_{in} + [O_2]_{PA})}{\gamma KT} + r \frac{(1 - \gamma)H([O_2]_{PA})}{\gamma KT}, \quad (1)$$

Notice that Eq. (1) encompasses both the supply and uptake of O_2 . The parameters of Eq. (1) are defined as follows:

- r is the ventilation/perfusion rate defined by the following piecewise linear function:

$$r = \begin{cases} 0.7 \left(\frac{t}{\tau_s} \right) & \text{if } t < \tau_s, \\ 0.7 & \text{otherwise,} \end{cases} \quad (2)$$

where t represents the duration of extrauterine life, and τ_s denotes the time necessary for the full expansion of the lungs. The variable r denotes the ventilation-perfusion ratio, which is modeled to increase linearly until reaching a stationary value of 0.7 within a time span of τ_s . After this point, the value of r remains constant at 0.7. This value serves as a gradual approximation of the value $r = 0.63 \pm 0.7$, which was observed in Koch's study after 24 h of extrauterine life [81]. Nonetheless, the time for the complete expansion of the lungs remains highly uncertain.

- ▶ $H([O_2])$ is the Hill Function defined as follows:

$$H([O_2]) = P_{50} \left(\frac{[O_2]}{1.34 \times [Hb] - [O_2]} \right)^{\frac{1}{2.7}}, \quad (3)$$

where P_{50} represents the partial pressure of oxygen at 50% saturation, and $[Hb]$ denotes the concentration of hemoglobin (Hb) in the blood.

- ▶ $[O_2]_I$ is the inspired oxygen concentration (also known as the alveolar oxygen concentration), which is calculated according to the following equation:

$$[O_2]_I = \frac{PAO_2}{KT}, \quad (4)$$

Eq. (4) was modified from [82] by incorporating the term PAO_2 , which represents the partial pressure of alveolar oxygen and is influenced by atmospheric pressure.

- ▶ $[O_2]_{PA}$ is the oxygen concentration in the pulmonary artery.
- ▶ γ is the respiratory efficiency (with values between 0 and 1).
- ▶ K is the ideal gas constant.
- ▶ T is the absolute temperature.

A more comprehensive explanation of gas exchange in the lung is provided in [83].

2.2.3. Reduced pulmonary vascular resistance

The initiation of pulmonary ventilation enables pulmonary gas exchange by increasing the partial pressure of oxygen (PO_2). This rise in PO_2 leads to a decrease in pulmonary vascular resistance [84]. Initially, this reduction is abrupt at the onset of pulmonary respiration. However, after a short period, it gradually continues over the following days to weeks [1]. The model developed in this study incorporates Eq. (5), sourced from Sá-Couto et al. [69], to represent the decrease in pulmonary vascular resistance as a function of the time elapsed since birth.

$$R_j(t) = \begin{cases} r_0(1 - 0.74(1 - e^{-6t})) & \text{if } 0 \leq t \leq 2h, \\ r_0(0.26 - 9.5 \times 10^{-4}(t - 2)) & \text{if } 2 \leq t \leq 24h, \end{cases} \quad (5)$$

where the index $i = 2, 3$ of R_j relates Eq. (5) with elements R_2 and R_3 of Fig. 2 which correspond, respectively, to the vascular resistance of pulmonary veins and arteries. In Eq. (5), r_0 is the initial pulmonary vascular resistance, and t is the time elapsed since birth in hours. Notice that, during the first two hours of life, Eq. (5) defines an exponential function that models the pulmonary vascular resistance. Subsequently, from 2 h to 24 h of life, Eq. (5) models the gradual decrease of pulmonary vascular resistance as a linear function.

2.2.4. Closure of the ductus arteriosus

Birth and the oxygenation of the blood initiate the closure of the ductus arteriosus. This event is essential for the successful adaptation to extrauterine life, as incomplete closure of the ductus arteriosus can potentially compromise the neonatal circulatory system [1].

Although the exact timing of ductus arteriosus closure remains uncertain [85], some studies suggest that functional closure occurs approximately between 12 and 48 h after birth [2,69]. In the study of Rasanen et al. [86], experimental values of changes in the diameter of the ductus arteriosus during the first 24 h of extrauterine life in humans are presented. The following equations, which were previously reported in Sá-Couto et al. [69], are used in this work:

$$D_{AD}(t) = 0.29 e^{-0.43t} + 0.30 e^{-0.054t}, \quad (6)$$

$$R_{13}(t) = \frac{K_a}{(D_{AD}(t))^4}. \quad (7)$$

Eq. (6) estimates the diameter of the ductus arteriosus (denoted as $D_{AD}(t)$) as a function of time. Eq. (7) is derived from Poiseuille's law

(as presented in [87]) and calculates the resistance of the ductus arteriosus (represented by R_{13} in Fig. 2) based on the diameter estimated in Eq. (6). The constant K_a in Eq. (7) corresponds to the value of 0.0145, mmHg s cm, which was chosen to calibrate the equation with the initial value of the vascular resistance of the ductus arteriosus. The variable t is the time elapsed since birth in hours.

2.2.5. Increased fetal systemic vascular resistance

The elimination of placental circulation begins at birth, resulting in an increase in fetal systemic vascular resistance [2], with an approximate doubling of its value [88]. This increase is initially rapid, followed by a more gradual rise [69], as represented by the following piecewise linear function:

$$R_7(t) = \begin{cases} 0.0846 t + 3.45 & \text{so } t_{cl} \leq t \leq 12h, \\ 0.00420 t + 4.42 & \text{if } 12h \leq t \leq 24h. \end{cases} \quad (8)$$

Eq. (8) represents an adapted version of the original expression presented in Sá-Couto et al. [69] in which we have included the term t_{cl} in hours, thereby allowing for the clamping of the umbilical cord at any given time. The variable t is the time elapsed since birth added to the time in which the umbilical cord was clamped in hours. In the model depicted in Fig. 2, the increase of fetal systemic resistance occurs in element R_7 , which represents the systemic peripheral vessels.

2.2.6. Completion of placental respiration

The placenta serves as the organ responsible for gas exchange in the fetus. During placental gas exchange, maternal blood flows through the intervillous space, carrying oxygen-rich blood. This flow enables the diffusion of oxygen molecules across the placental barrier and into the fetal systemic circulation [89]. The fetus remains connected to the placenta via the umbilical cord, which comprises one umbilical vein and two umbilical arteries. The umbilical vein transports oxygenated and nutrient-rich blood from the placenta to the fetus, while the umbilical arteries carry nutrient-poor, deoxygenated blood from the fetus to the placenta [89]. A more comprehensive explanation of placental respiration is provided in the supplementary material [83]. In the proposed model of this study, the diffusion of oxygen molecules or the oxygen concentration entering the fetal systemic circulation from the placenta is called $[O_2]_{in}$ and occurs within the umbilical vein (labeled R_{12} in Fig. 2). The following equation describing $[O_2]_{in}$ is taken from Yigit et al. [67]:

$$[O_2]_{in} = r[O_2]_U - rH_M^{-1} \left(\frac{H([O_2]_{in} + [O_2]_{PLAC})}{\gamma} + \frac{(1 - \gamma) + [O_2]_{PLAC}}{\gamma} \right). \quad (9)$$

The terms of Eq. (9) are defined as follows:

- ▶ r is the ventilation/perfusion rate defined by the following equation:
- $$r = \frac{600 \text{ ml/min}}{Q_{plac}}, \quad (10)$$
- ▶ Q_{plac} refers to fetal placental flow. The influx of placental $[O_2]$ into the fetus is regulated by Eq. (10) (adapted from Yigit et al. [67]). This equation illustrates the association between fetal placental flow and maternal blood flow to the placenta, typically ranging from 600 to 700 mL/min [89].
 - ▶ $[O_2]_U$ is the concentration of uterine oxygen.
 - ▶ H_M^{-1} represents the inverse of the maternal Hill function. A detailed description of this function can be found in the supplementary material [83]. The maternal Hill function is defined as follows:

$$H_M^{-1} = \frac{(1.34 * [Hb]) \left(\frac{H([O_2])}{P_{50}} \right)^{2.7}}{1 + \left(\frac{H([O_2])}{P_{50}} \right)^{2.7}} \quad (11)$$

where P_{50} represents the partial pressure of oxygen at 50% of saturation, $[Hb]$ denotes the concentration of Hb in the blood, and $H([O_2])$ represents the fetal Hill function defined by Eq. (3).

- ▶ $[O_2]_{PLAC}$ refers to the concentration of oxygen (O2) in the placenta.
- ▶ γ is the respiratory efficiency, which assumes values between 0 and 1.

2.2.7. Elimination of placental circulation by the UCC

The occurrence of UCC in a newborn results in interruption of blood flow to and from the placenta. This abrupt cessation of blood flow within the umbilical cord, as observed in some reported cases of Early Cord Clamping (ECC), could have serious implications for the newborn. Additionally, elimination of the placental circulation leads to a significant increase in the resistance of the umbilical vein and umbilical arteries, making their resistance value extremely high. Consequently, the flow of blood to and from the placenta is impeded. To express the increase in vascular resistance, we propose the following equation:

$$R_{1j}(t) = \begin{cases} r_i & \text{if } t \leq t_c, \\ r_i e^{kt} & \text{if } t_c < t \leq \tau_o + t_c, \\ r_f & \text{else } \tau_o + t_c < t, \end{cases} \quad (12)$$

where index $j = 1, 2$ of R_{1j} relates Eq. (12) with components R_{11} (representing umbilical arteries) and R_{12} (representing the umbilical vein) in Fig. 2. In Eq. (12), $k = \ln(r_f/r_i) \times \tau_o$. t is the simulation time in seconds from the moment of clamping the umbilical cord. t_c represents the time in seconds at which UCC is performed. τ_o represents the short time in seconds it takes for complete occlusion of both umbilical arteries and the umbilical vein after umbilical cord clamping based on time (ECC or DCC). In Eq. (12), the values of r_i and r_f correspond, respectively, to the initial and final values of the umbilical veins and arteries. From a computational point of view, setting r_f to ∞ is impossible. Therefore, we have set the value of r_f to be eight orders of magnitude greater than that of r_i .

2.3. Transition from fetus to neonate at different heights

The transition from fetus to neonate is regulated by the availability of oxygen in the environment, leading to differences in birth outcomes between high altitude and sea level births [71]. Studies have shown that a decrease in the partial pressure of oxygen PO_2 in alveolar air is associated with an increase in pulmonary vascular resistance [90]. A study of 200 neonatal births 200 m above sea level in [90] concluded that the evaluation of pre- and postductal oxygen saturation SO_2 at different altitudes is necessary to accurately evaluate neonatal well-being. Other studies, such as [91,92], have shown that a fetal weight loss of 17%–21% can be attributed to low fetal arterial oxygen saturation. Furthermore, chronic hypoxia resulting from high-altitude living, as highlighted in [93], can not only retard fetal growth but also increase perinatal mortality.

To evaluate the effects of altitude on the cardiovascular and respiratory transition, the following two equations have been integrated to the model:

$$P_{atm} = P_0 e^{(-mg/KT)h} \quad (13)$$

$$PAO_2 = (P_{atm} - PH_2O)FiO_2. \quad (14)$$

Eq. (13) (taken from [94]) defines the atmospheric or barometric pressure, denoted as P_{atm} . The parameters of Eq. (13) are defined as follows: P_0 represents the pressure at sea level, m denotes the mass of a molecule, g signifies gravity, K represents the gas constant, T indicates room temperature, and h represents the altitude in meters above sea level.

Eq. (14) (taken from [95]) defines the partial pressure of alveolar oxygen,⁶ which is denoted as PAO_2 . In this equation, PH_2O refers to the partial pressure of water (47 mmHg), and FiO_2 represents the fraction of inspired oxygen. It is worth noting that PAO_2 is computed in the element labeled as h_1 in the model shown in Fig. 2.

Furthermore, it is important to emphasize that Eqs. (13) and (14) are interconnected with the neonate’s hemodynamic and respiratory systems. These equations are specifically included to determine the partial pressure of oxygen in the environment where the neonate breathes.

3. Results

In this section, we will use the simulator to conduct a simulation analysis of transitions at birth and the effect of UCC timing.

3.1. Simulation of transitions at birth and due to UCC

Fig. 3 illustrates the changes in systemic arterial pressure and vascular resistance of the ductus arteriosus resulting from birth and UCC. In Fig. 3(a), it can be observed that arterial blood pressure changes at 600 s after birth due to UCC.

The increase in systemic pressure is attributed to occlusion of the umbilical vein and arteries, as well as increased fetal systemic resistance. The reduction in pulmonary pressure shown in Fig. 3(a) is the result of decreased pulmonary resistance during birth. Regarding the ductus arteriosus (DA), Fig. 3(b) presents the change in its vascular resistance, on a logarithmic scale, during the first 24 h of postnatal life.

Figs. 4 and 5 show the changes in systemic, pulmonary, and umbilical vascular resistance from birth and during UCC. In Fig. 4, on a logarithmic scale, the changes in pulmonary vascular resistance (peripheral vessels and pulmonary vein) and systemic vascular resistance (systemic peripheral vessels) are evident.

In Fig. 5, an example of the behavior of the umbilical arteries and the umbilical vein, on a logarithmic scale, is observed. The final resistance value of the umbilical arteries has been set as twice the resistance value of the umbilical vein to signify that in the umbilical cord, there are two umbilical arteries and one umbilical vein. The value of τ_o has been set to 100 s for this Fig. 5 in order to illustrate the exponential behavior of Eq. (12) proposed in this study.

In the simulator developed for this study, it is assumed that the components representing vascular resistance, heart valves, and inertia do not accumulate blood or consume oxygen. The metabolic consumption rates of the other components have been derived from the book by Rudolph [96].

3.2. Analysis of UCC timing using simulation

One of the most debated aspects in the study of the timing of UCC is the placental transfusion and the volume of blood that the organs receive in the first moments of extrauterine life. Kakkilaya et al. [97] state that performing UCC at birth leaves the neonate with a blood volume similar to that it had in utero, while delaying UCC facilitates the placental transfusion of additional blood to the neonate, as evidenced by Refs. [26,38,41,98–101]. Guyton [88] notes that the neonate has around 300 ml of blood at birth, but if the neonate is left attached to the cord a few minutes after birth, it can gain approximately 75 ml of extra blood. After a few hours, this additional volume is lost, but the increase in hematocrit (HCT) remains. HCT is a measure of the volume of red blood cells (RBCs) as a percentage of total blood volume [102]. Maintaining normal HCT volumes is extremely important since a reduction in RBCs causes anemia [103].

⁶ The term related to carbon dioxide has been eliminated from this equation.

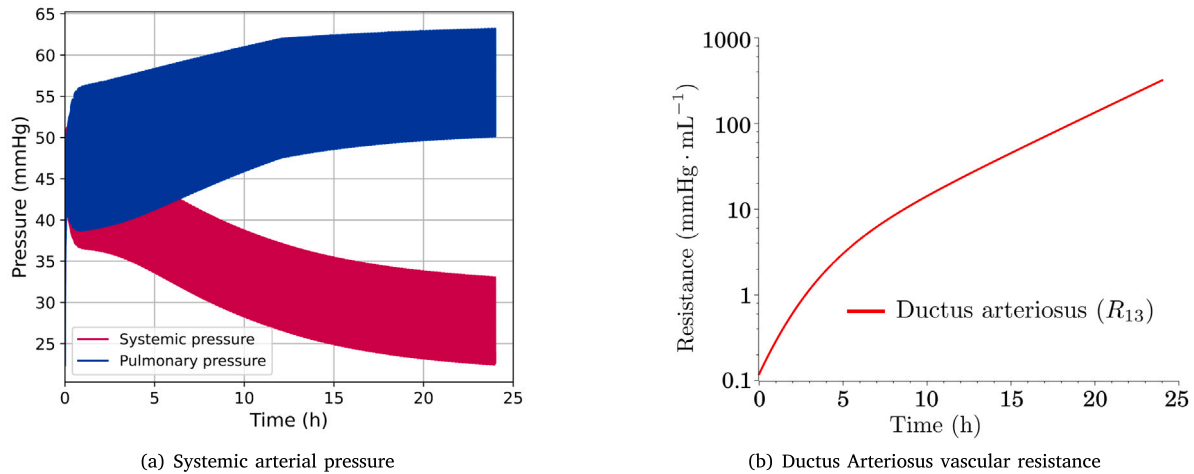


Fig. 3. Changes in arterial pressures and ductus arteriosus by UCC and birth.

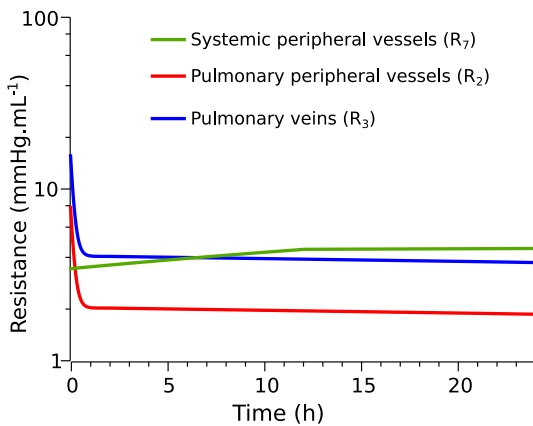


Fig. 4. Pulmonary and systemic vascular resistance.

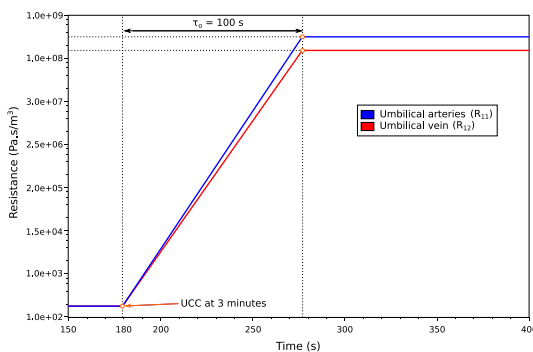


Fig. 5. Umbilical vascular resistance.

Furthermore, a reduction in RBCs leads to a decrease in hemoglobin (Hb) levels. Hb is a protein found in red blood cells that binds to oxygen in the lungs and carries it through the bloodstream to the tissues of the body [104]. In other words, the greater the number of red blood cells, the more hemoglobin is present in the blood, thereby potentially increasing the overall capacity for oxygen transport.

In the same way, another important factor to consider when making decisions regarding the appropriate time of UCC is the oxygen saturation of the newborn (SO_2). Oxygen saturation is considered an indicator of progress in neonatal adaptation [105]. Studies such as those presented in Refs. [106–108] demonstrate a significant difference in SO_2 depending on the timing of UCC, with delayed cord clamping resulting

in an increase in SO_2 compared to immediate or early clamping of the umbilical cord.

The altitude at which birth occurs also influences oxygen saturation, and therefore the concentration of oxygen available in the environment is another important factor when performing UCC. Niermeyer [71] notes that the cardiopulmonary transition at high altitudes differs from that at sea level due to the concentration of oxygen available.

Due to the reasons mentioned above, we will now take a preliminary step in the analysis by simulating the clinical practice of UCC.

The purpose of this analysis is to enhance our understanding of the effects of performing UCC at different time points and under varying altitude conditions. To achieve this goal, we present three simulated scenarios: (SC1) The effect of the time of the UCC on placental transfusion and the blood volume supplied to the organs in the first moments of extrauterine life; (SC2) The effect of time of the UCC on oxygen saturation; and, (SC3) The effect of altitude on oxygen saturation at birth.

(SC1) Effect of UCC timing on placental transfusion

Numerous studies have attributed various benefits to placental transfusion in neonatal adaptation (see Refs. [13,37,38,41,88,109–111]). However, it is important to note that several other studies have pointed out some adverse effects associated with placental transfusion (see [112,113]).

To perform the simulated analysis of placental transfusion, we use the model in Fig. 2 to perform UCC at different times. Initially, UCC was performed every 5 s for the first 5 min after birth, and then changed to a frequency of once per minute until the 10th minute. The first 10 min of life were specifically chosen due to their critical role in neonatal adaptation. The red curve with diamonds in Fig. 6 connects the outcomes of these 65 experiments, with each dot representing a single experiment. This curve represents the additional blood volume obtained by the neonate through placental transfusion after UCC (Umbilical Cord Clamping). The volume ratio between placental and fetal blood for a neonate weighing 3445 g at birth is derived from the study conducted by Kakkilaya [97].

It is important to stress that the relative position of the infant and placenta (i.e., the gravity) affects the hemodynamics of the neonate [114] and the placental transfusion [115], depending on the timing of UCC [116]. This factor is not included in the current model, which assumes that the newborn is positioned in the perineal plane, resulting in no net hydrostatic pressure.

Notice the magenta points in Fig. 6 that highlight seven specific time instants ($t = 0$ s, 30 s, 60 s, 90 s, 120 s, 180 s and 300 s). According to the review shown in Fig. 1, they are key points for defining UCC.

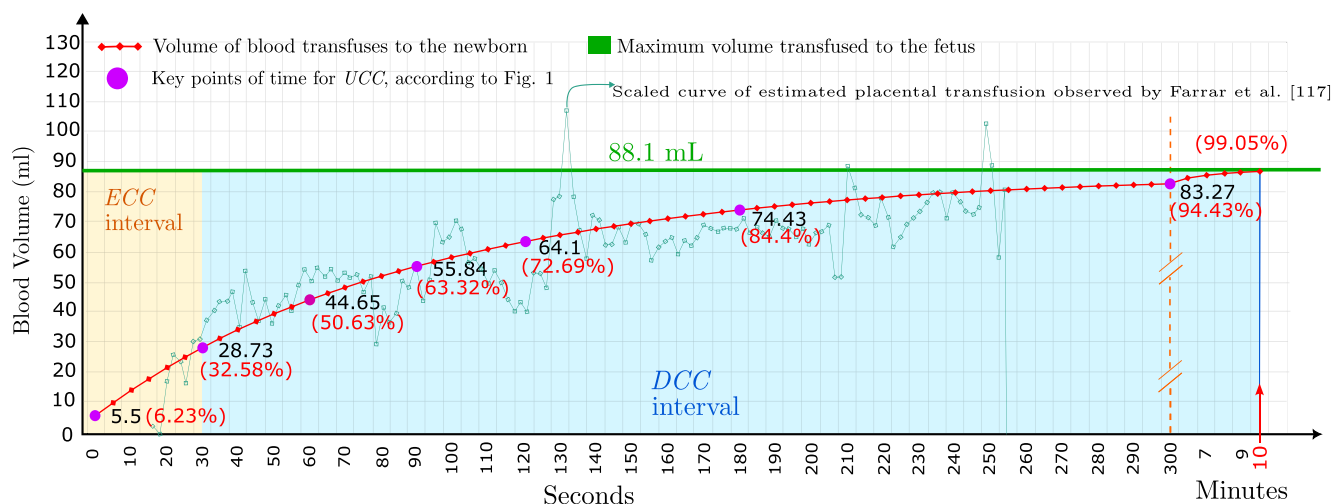


Fig. 6. Neonate's gain in blood volume from placental transfusion.

As shown in Fig. 6, the gain in blood volume of the newborn increases depending on the timing of UCC. The green line represents the upper limit for the simulated volume of placental blood that can be transferred to the neonate, measuring⁷ 88.1 mL. This value falls within the average range of 69 to 152 mL as reported by Farrar et al. [117].

By examining the first 5 min of extrauterine life, it becomes evident that the changes in transfused blood volume are significant. For instance, when the cord is clamped at birth, it prevents the neonate from receiving 93.76% of the extra blood available in the placenta. Similarly, performing UCC at 30 s (as recommended by the AAP [34] and the ACOG [5]) results in a gain loss of 67.41%, at 60 s (as recommended by the WHO [33]) a loss of 49.4%, at 90 s a loss of 36.6%, at 120 s a loss of 27.3%, and finally, performing UCC at 3 min prevents the neonate from receiving approximately 16% of the remaining placental blood.

To compare the simulated behavior of placental transfusion with clinically observed values, Fig. 6 includes an observed curve from Farrar et al. [117]. They used the newborn's weight⁸ for estimating the volume of blood transferred from the placenta. The observed curve has been adjusted to correspond to a final value of 80 mL (at 255 s) to facilitate comparison of trends and relative increases in blood volume from placental transfusion. The initial artifact indicated by the authors has been removed. The time scale remains unchanged.

Remark 1. From the simulation results condensed in Fig. 6, it is important to notice the following facts: (i) the average placental transfusion rate in the ECC interval is about 1 mL/s; (ii) by 3 min of life, the neonate has received a significant amount of placental blood (74.43%); (iii), by 5 min nearly the maximum blood volume from the placenta (94.4%); (iv) by 10 min, the neonate has received practically the entire placental blood volume (99%).

(SC2) Effect of UCC timing on oxygen saturation

Several studies have been conducted to assess the impact of different timings of UCC on oxygen saturation (SO_2) levels (see [58,118,119]). Maharaj et al. [105] highlight that oxygen saturation is an essential metric measured in the delivery room, providing insight into the neonate's adaptation to extrauterine life.

⁷ It is important to stress that this value is by no means a precise figure. Rather, it is used here as a reference point to understand the relative increase in blood volume from placental transfusion that can be expected when the UCC is delayed.

⁸ Notice that this method results in a record of plenty of artifacts due to the baby's movements and the ongoing neonatal care procedures.

To set the context for this scenario, we introduce the term Physiological-Based Cord Clamping (PBCC), which can be described as a clinical practice that prevents the loss of potential support from placental circulation that occurs in healthy term or late preterm newborns. This loss typically occurs because these babies are often subjected to ECC, as described in [120]. In general terms, PBCC involves clamping the umbilical cord not when the newborn begins to breathe, but after establishing aeration and pulmonary ventilation, as discussed in [121]. This clamping has shown promising results as a readily available means to improve early infant outcomes by allowing adequately established pulmonary circulation and resulting in a more stable circulatory transition [121]. PBCC has demonstrated improvements in cardiovascular stability and reduced hypoxia [120]. Some studies have shown that performing PBCC compared to ECC would result in a higher heart rate (HR) in babies in need of resuscitation, without compromising safety [120].

Now we are ready to evaluate UCC at five distinct points in time: (i) early cord clamping (ECC) performed just at birth; (ii) ECC at 30 s; (iii) delayed cord clamping (DCC) performed at 60 s; (iv) DCC at 2 min; and, (v) physiological-based cord clamping (PBCC) with complete establishment of pulmonary ventilation, aeration, and a nearly complete net placental transfusion. To simulate an upper bound of physiological-based cord clamping, we assume that achieving complete lung expansion requires 24 h (it is defined by the parameter τ_s in Eq. (2)). Therefore, we also perform a hypothetical UCC at 24 h.⁹

Fig. 7 illustrates the oxygen saturation levels in the pulmonary arteries for each clamping point. It is important to interpret the 90-min interval on the time axis in Fig. 7 in a comparative manner, considering that, in this extreme scenario, both complete lung expansion and UCC take place at 24 h.

Consider the pink area between the magenta and the violet curves, which represent the oxygen saturation levels with ECC at birth and DCC at 30 s, respectively. This area illustrates the enhancement in neonatal adaptation achieved by delaying UCC within the 30-s interval of ECC. Since the rate of placental transfusion peaks within this interval (refer to Fig. 6), conducting ECC close to the 30-s mark allows the newborn to achieve the 95% saturation level earlier – by up to 3.2 min on this comparative time scale – as compared to ECC at birth.

Now consider the light blue area between the violet curve and the solid blue curve representing the oxygen saturation level for DCC at 120 s. This area indicates that delaying UCC beyond 30 s results in

⁹ This duration was determined by considering physiological studies and also by ensuring that the simulation itself achieves steady-state conditions.

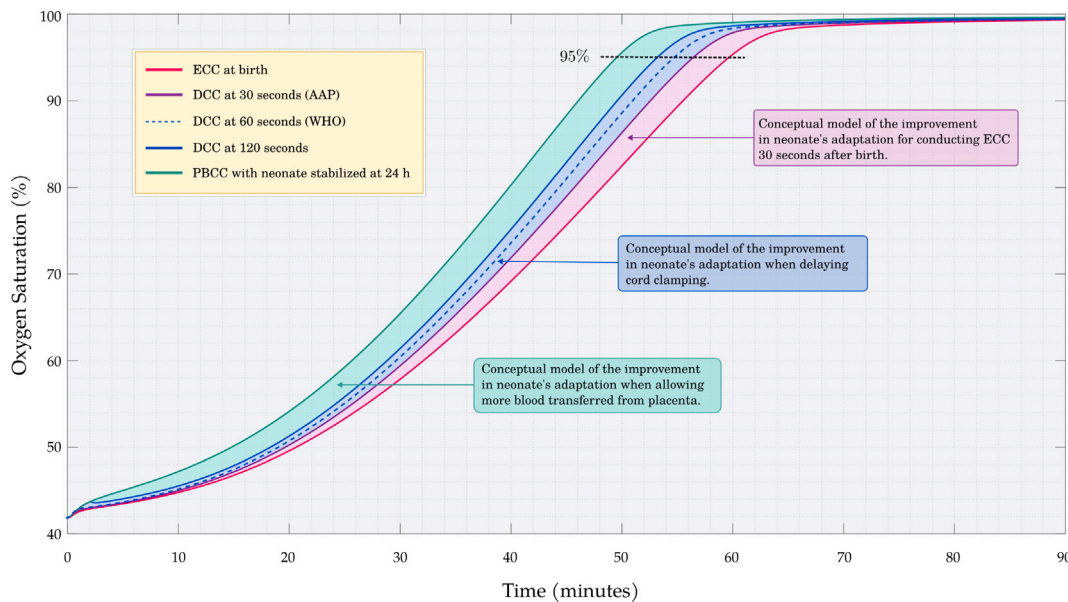


Fig. 7. Oxygen saturation levels of the pulmonary arteries for PBCC, DCC and ECC (see [122]).

further improvement in neonatal adaptation. Additionally, there is a noticeably faster response in oxygen saturation when performing DCC at 60 s (in line with WHO recommendation [33]) compared to ECC at 30 s (as advised by the AAP [34] and ACOG [5]).

Finally, consider the light green area between the solid blue curve and the green curve representing the oxygen saturation level for PBCC. This area clearly shows the advantage in neonatal adaptation that can be achieved by ensuring that the neonate meets all stabilizing conditions, including nearly complete placental transfusion, prior to cord clamping.

Remarkably, within this comparative time scale, conducting PBCC allows the neonate to reach the 95% saturation level 3.6 min earlier than with DCC at 120 s, 6.8 min faster than with DCC at 30 s, and ten minutes sooner than with ECC at birth.

Remark 2. The simulation results for this scenario suggest that neonates who undergo DCC, and particularly those who undergo PBCC, attain higher oxygen saturation levels in a shorter period of time.

Remark 2 aligns with the clinical study conducted by Ashish et al. [123]. However, the establishment of pulmonary respiration does not depend solely on the type of clamping performed on the newborn but also on the birth altitude, as evaluated in the following scenario.

(SC3) Effect of altitude on available oxygen at birth

The variables of respiratory rate, heart rate, and oxygen saturation are affected by birth at high altitudes [124,125]. During birth, the pulmonary circulation undergoes a transition to a low resistance state, enabling a high blood flow condition in neonates. Alongside this change, alveolar ventilation is initiated through an increase in alveolar PO_2 [126].

Let us now revisit Eqs. (13) and (14). The latter demonstrates a direct relationship between alveolar PO_2 and atmospheric pressure (P_{atm}) which, in accordance with Eq. (13), depends directly on the height above sea level.

For this scenario, we conduct a simulated analysis of ECC and PBCC at three different heights above sea level: Lhasa (China) at 3650 m, Popayán (Colombia) at 1760 m, and Lisboa (Portugal) at sea level (0 m). The duration τ_s , necessary for complete lung expansion, as defined in Eq. (2), is established at 30 min to fit the clinically reported typical oxygen saturation stabilization time of 10 min for newborns at low

altitude. Fig. 8 shows the simulated oxygen saturation values obtained when performing ECC and PBCC in the three cities.

Consider first the oxygen saturation values obtained with ECC, depicted as the dark-colored sections at the bottom and within each bar in Fig. 8. There is a noticeable delay in the stabilization of pulmonary respiration at high altitudes, as observed in Lhasa, compared to ECC at sea level. In high-altitude cities like Lhasa and Popayán, it can take newborns more than 10 min to achieve an oxygen saturation level above 95%. In contrast, in lower-altitude cities such as Lisboa, oxygen saturation levels exceed 95% within 9 min. At the same time, in Popayán, the saturation level is 71.5%, and in Lhasa, it is 63.6%, thereby indicating a more critical situation.

Consider now the oxygen saturation levels achieved with PBCC, depicted as the lighter-colored sections at the top and within each bar in Fig. 8. Notice that at Lisboa's altitude, the oxygen saturation level surpasses 95% within just 7 min, whereas in the other two cities, achieving similar levels requires up to 10 min.

Comparatively, we can notice that PBCC induces the onset of pulmonary respiration within 7 min for births at sea level and within 10 min for births at higher altitudes. Conversely, ECC induces this process in 9 min at sea level, although it can take considerably longer at higher altitudes.

Remark 3. The simulation results for this scenario indicate that allowing for the stabilizing conditions of PBCC notably improves the onset of pulmonary respiration as compared to ECC. The benefit of PBCC for neonatal adaptation is more decisive for newborns at high altitude.

4. Discussion

This study introduces a simulator that can model changes in the cardiovascular and respiratory systems of a newborn during birth and as a consequence of UCC, as illustrated in Figs. 3(a), 3(b), 4, and 5.

Taking into account the accuracy of the model in representing pressures, Table 2 presents the concordance between the simulated blood pressure values for newborns and the clinically reported values. The pressure measurements in Table 2 were taken from the “Pulmonary Arteries” and “Intrathoracic Arteries” elements in Fig. 2 after 24 h post-birth, following a clamping of the umbilical cord performed at 10 min (600 s). This is noteworthy, considering the number of model's

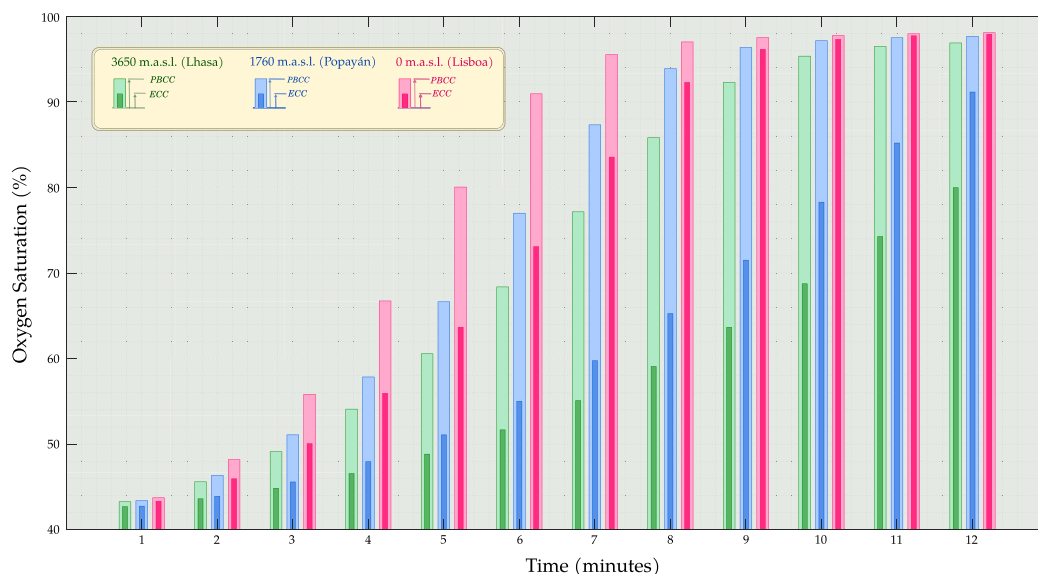


Fig. 8. Arterial oxygen saturation with ECC (at birth) and PBCC at different heights above sea level during the first 12 min of extrauterine life.

Table 2

Comparison between blood pressures obtained by simulation and clinically reported values.

Pressures (mmHg)	Reference value	Simulated value	Reference
Systolic arterial systemic	73.3 ± 7.5	63.1	[127]
Diastolic arterial systemic	49.6 ± 5.2	50.1	[127]
Systolic pulmonary systemic	43.83 ± 7.90	33	[128]
Diastolic pulmonary systemic	19.70 ± 8.51	22.4	[128]

parameters and the diversity of sources from which they were derived (see Refs. [69,73]).

The first factor considered in this study is the *placental transfusion*. In this regard, Fig. 6 shows that the fetus receives 94.43% (83.27 mL) of placental blood after 5 min of extrauterine life. The simulated in utero blood volume of the neonate is 241.15 mL. These results align with the clinical values reported in [117].

According to Fig. 1, clamping at birth and within 30 s are both classified indistinctly as Early Cord Clamping (ECC). Nonetheless, there is a notable 26.35% difference in the volume of blood transfused to the neonate within this timeframe. It is also important to note that the rate of blood transfusion during this critical period averages at 1 mL/s. As demonstrated in Fig. 7, this significantly enhances and accelerates neonatal adaptation.

When the UCC is performed in 30 s (according to the conservative interpretation of the AAP's suggestion), the neonate receives only 32.58% of the available blood, while in the DCC at 5 min scenario, the neonate receives 94.43% or more. The 61.85% difference in extra blood can significantly improve and accelerate neonatal adaptation as clearly shows Fig. 7.

As depicted in Fig. 6, the amount of blood transfused to the newborn during the first minutes of life (within the first 5 min after birth) undergoes a drastic change. Consequently, the conventional time-oriented classification of ECC and DCC presented in Fig. 1 is completely inadequate for accurately assessing the effects of UCC. Therefore, conducting research on physiology-based cord clamping PBCC is of paramount importance to guarantee optimal care for the newborn.

Placental transfusion has been attributed with various beneficial effects, including a *reduction in the number of blood transfusions due to anemia* [13,38,41,109], *improvement in blood pressure* [109,110], *decrease in intraventricular hemorrhage* [13,111], *reduction in late-onset sepsis and improvement in immune status due to transfusion of hematopoietic progenitor cells* [13,111]. Furthermore, as mentioned in [37], placental

transfusion increases the circulating blood volume at birth, thereby improving the hemodynamic status of premature newborns. It is also an extremely effective method to improve arterial oxygen content, cardiac output, and oxygen supply [129].

A second relevant factor evaluated in this study is the *effect of UCC timing on oxygen saturation*. In this regard, Fig. 7 shows that the time it takes for a newborn to reach adequate levels of oxygen saturation is prolonged when the umbilical cord is clamped at birth. The earlier umbilical cord clamping (UCC) is performed, the more time the newborn requires to establish pulmonary respiration.

The third significant factor evaluated in this research is the *effect of altitude on available oxygen at birth*. In this regard, Fig. 8 illustrates the umbilical cord clamping performed at birth at three different altitudes. As depicted in the figure, achieving establishment of pulmonary respiration and adequate levels of oxygen saturation within the first 10 min of extrauterine life is only feasible when the neonate is born in a location close to sea level.

Fig. 8 shows the simulated PBCC performed at three different altitudes. Notice that approximately 7 min after birth, the oxygen saturation value starts to stabilize at sea level, while for Lhasa (at 3650 m above sea level) and Popayán (at 1760 m above sea level), stabilization occurs at 9 and 10 min, respectively. These findings are consistent with the results of the study of Valero et al. [124], which evaluates the adaptation in 59 newborns at 3828 m above sea level, showing that respiratory and cardiac frequency, as well as oxygen saturation (initially low), start to stabilize at 10 min and reach equilibrium within 6 h.

It is worth emphasizing that individuals living in high altitudes are physiologically adapted to these environments [130]. However, altitude of birth must be taken into account when performing the UCC since the closure of fetal shunts and vascular changes in general may take longer [71,124]. As highlighted in Remark 3, this simulation study suggests that performing PBCC can notably enhance the establishment of pulmonary respiration, thereby potentially preventing the neonate from experiencing the adverse effects of birth at high altitudes¹⁰

Concerns have long been expressed that clinical conditions like symptomatic polycythemia and hyperbilirubinemia are associated with DCC (this concern also applies to PBCC).

¹⁰ According to [131], birth at high altitudes can lead to pulmonary hypertension and chronic hypoxia, while [132] states that the risk of pre-eclampsia increases with altitude.

Hyperbilirubinemia occurs due to elevated levels of bilirubin in the blood. Bilirubin is a product of red blood cell breakdown, and its accumulation in the body can lead to jaundice, characterized by a yellowing of the skin and eyes. On the other hand, polycythemia results from an abnormal increase in the number of red blood cells in the blood.

However, as noted in several studies [133–138], there is not substantial evidence indicating an increased risk of hyperbilirubinemia or symptomatic polycythemia due to delayed cord clamping. In a recent study, Andersson and Mercer [8] examined systematic reviews and meta-analyses that ranged from 2007 to 2020. They found no current evidence supporting this concern and, notably, no literature reporting on symptomatic polycythemia. These findings further reduce the list of potential contraindications for adopting clamping techniques that allow for an increased transfer of blood to the newborn, such as *DCC* or *PBCC*.

5. Limitations of the study

As mentioned throughout the study, the computational calculations and experiments were conducted under the assumption of a healthy full-term newborn birth. Therefore, the results may not be directly applicable under other scenarios. In general, medical guidelines have evolved towards delayed cord clamping (*DCC*) in healthy term newborns, as it has been demonstrated to have benefits in terms of blood and oxygen transfer to the baby, as consistent with the results presented in this study. However, in specific medical situations, early cord clamping (*ECC*) may be necessary to address critical issues. For instance, taking into account the contraindications for *DCC* in term newborns presented in Table 1, or scenarios such as emergency cesarean section, problems with fetal blood flow, such as fetal bradycardia (low heart rate), or the need for immediate resuscitation, where the newborn requires prompt resuscitation, including ventilation or cardiopulmonary resuscitation. In all such situations, early cord clamping can be crucial in the adaptation of the newborn to extrauterine life. Finally, this study does not assume compensatory mechanisms that can modify the level of oxygen saturation of individuals at different heights above sea level. These mechanisms will be explored in Future work.

6. Future work

The continuation of this study will be divided into two parts. Firstly, we will undertake new computational developments to extend and enhance the model. Within these computational explorations, we will evaluate the use of advanced solvers in Functional Mock-up Units (FMU), different programming languages for integrating graphics and animations with high frame rates, eliminating the need for users to install multiple tools to use the physiological simulator. We aim to integrate the proposed model, an example called *Fetus2neonate_transition*, into the library called “PatientEvoPhysio”, which is still under development. This integration will not only facilitate research on umbilical cord clamping, but also allow for the analysis of anomalies in the cardiovascular and respiratory systems, as well as the effects of various clinical practices in adults, children, newborns, and fetuses. This collaborative effort is motivated by the ethical limitations associated with conducting critical experiments on living beings, making these tools an intriguing alternative. We welcome external code contributions. In its final version, this model will become one of the many scenarios available in the library, easily accessible from a Web browser without the need for additional installations. All updates of this research will be regularly published in the **GitHub** (<https://github.com/ehsepulvedao/PatientEvoPhysio>) and **Zenodo** (<https://zenodo.org/records/10054996>) [139] repositories.

On the other hand, a significant effort will be made in collaboration between engineering and medical specialists to formally extend the foundational physiology model presented in this study. Furthermore, we are currently looking for solid collaborations with researchers and

other institutions that allow to evaluate the computational library (PatientEvoPhysio) used in this study, especially in terms of compatibility with other licensed compilers, such as Dymola. In addition, advanced computational studies, such as the one carried out in [140], will be carried out for the BIG DATA medical analysis that allows extracting hidden information to complement the protocol described in this study.

In our ongoing efforts to enhance the functionality and efficiency of web simulators in our project, we have identified a promising direction for future development. Inspired by valuable feedback, we are exploring the integration of OpenModelica’s Functional Mock-up Interface (FMU) with the CVODE solver export. This approach has the potential to significantly streamline the patient evoPhysio deployment process of our library. Our objective is to investigate how the FMU with CVODE export, known for its robustness in handling complex differential equations, can reduce the computational workload and improve the overall performance of our simulator. This exploration is a part of our commitment to continually evolve our project by incorporating advanced methodologies and tools.

It should be noted that the model presented in this study is applicable to cases of healthy term newborn deliveries. However, although this computational model represents a significant initial advancement in the investigation of the objective effects of the umbilical cord clamping, without complications or interventions on living beings, we are aware of multiple aspects that need to be incorporated to improve its level of representation of the real condition of the newborn. For example, in future work, aspects such as the relative position of the infant and placenta (*i.e.*, the effects of gravity on placental blood flow) will be evaluated.

Similarly, the system will be linked to a discrete event system that can monitor clinical evolution and make decisions based on states and transitions derived from metrics such as the APGAR score.¹¹ Furthermore, another set of clinical practices and systems will be evaluated for inclusion in the model, including medication administration. Additionally, multiple scenarios with possible complications for unhealthy newborns will be evaluated using various types of umbilical cord clamping. Finally, compensatory mechanisms of oxygen saturation in individuals born at different heights above sea level will be explored.

7. Conclusions

The contribution of this document lies in the development of simulation models and the collection of quantitative data to analyze the neonatal evolution after birth. It also explores the impact of clinical interventions like the *moment of the UCC* and heart disease scenarios as presented in [64]. This research tool allows for evaluating a shift from time-based clamping to physiological-based clamping (*PBCC*) for the first time using simulation. Furthermore, the simulator introduced in this study facilitates investigations similar to the one proposed in Ref. [142], which focuses on assessing conditions such as the initiation of ventilation and *UCC* to study the potential benefits of resuscitation with an intact cord.

By studying clinical practices through the use of simulation methodologies, it is possible to perform various interventions on newborns without causing them any harm [143]. Although these simulators do not accurately represent physiological responses to different interventions or birth conditions, they serve as a basis for a general understanding of the phenomena occurring in newborns.

Based on the results of Fig. 6, it can be deduced that *ECC* brings adverse effects on the hemodynamic and respiratory components of an individual. In contrast, *DCC* has a significant beneficial impact on the hemodynamics of the newborn, mainly due to improved blood volume and sustained placental respiration. Delayed or physiologically based

¹¹ The Apgar scale is employed for assessing the vitality and progression of the newborn during various stages of the neonatal adaptation process [141].

cord clamping allows the placenta to supply the newborn with about a blood supply, as shown in this research and reported in [144].

It is important to note that the results presented in this work justify further in-depth research that can define and standardize physiological criteria for neonates, determining the appropriate moment to perform *UCC* based on these criteria rather than relying solely on time. This is necessary due to the impact of various factors, such as birth altitude, which hinder the uniform standardization of clamping time. Individualized analysis of the newborn is required to identify the ideal moment for *UCC*. The work presented in this study could serve as a valuable addition to the formal discrete models of medical procedures, as discussed in previous studies such as [143,145]. It is important to clarify that while the results presented in this study are limited to a scenario of healthy full-term newborns, they can make a meaningful contribution to the discussion of the appropriate timing of *UCC*.

Based on the findings of this research, it can be concluded that an extensive study is necessary to explore the benefits or adverse effects of neonatal resuscitation with delayed clamping, which allows for the maximum volume of blood to be obtained from placental transfusion. This extended study should also consider factors such as humidity, temperature, gravity,¹² and other conditions that influence the partial pressure of alveolar oxygen and the vasoconstriction of fetal shunts.

With the progress made in this study, it is expected that healthcare professionals can conduct research to accelerate consensus processes and the development of protocols and clinical guidelines that improve newborn care.

CRedit authorship contribution statement

Edgar Hernando Sepúlveda-Oviedo: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Leonardo Enrique Bermeo Clavijo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Luis Carlos Méndez-Córdoba:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Friedman A, Fahey J. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. *Semin Perinatol* 1993;17(2):106–21.
- [2] Rudolph A. The changes in the circulation after birth. Their importance in congenital heart disease. *Circulation* 1970;41(2):343–59.
- [3] Ninia KA, Ashmauey AA, Qahtani NHA. Effect of early and late clamping of the umbilical cord on the newborns blood analysis. *J Nurs Health* 2017;02.

¹² The influence of gravity on placental transfusion remains not completely understood. The study of Vain et al. [146] observed no significant difference in placental transfusion for neonates subjected to a 2-min *DCC*, regardless of whether they were placed on the maternal abdomen or at the mother's perineum. Complementarily, the study by Merger et al. [147] found that neonates placed on the maternal abdomen immediately after birth and subjected to a 5-min *DCC* received larger placental transfusion compared to those with a 2-min *DCC*. In any event, the placental transfusion rate constitutes an essential factor that deserves further research attention.

- [4] Rabe H, Gyte G, Díaz-Rossello J, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2019;09(09):CD003248.
- [5] Opinion AC. Delayed umbilical cord clamping after birth: ACOG committee opinion summary, number 814. *Obstet Gynecol* 2020;06(136):1238–9.
- [6] Mohammad K, Tailakh S, Fram K, Creedy D. Effects of early umbilical cord clamping versus delayed clamping on maternal and neonatal outcomes: a Jordanian study. *J Matern-Fetal Neonatal Med* 2021;02(34):231–7.
- [7] Okulu E, Haskologlu S, Guloglu D, Kostekci E, Erdev O, Atasay B, Koc A, Soylemez F, Dogu F, Ikinogullari A, Arsan S. Effects of umbilical cord management strategies on stem cell transfusion, delivery room adaptation, and cerebral oxygenation in term and late preterm infants. *Front Pediatr* 2022;10(838444):PMC9013943.
- [8] Andersson O, Mercer JS. Cord management of the term newborn. *Clin Perinatol* 2021;48(3):447–70.
- [9] Kinmond S, Aitchison T, Holland B, Jones J, Turner T, Wardrop C. Umbilical cord clamping and preterm infants: a randomized trial. *Br Med J* 1992;306(6871):172–5.
- [10] Hofmeyr GJ, Gobetz L, Bex PJ, Van der Griendt M, Nikodem C, Skapinker R, Delahunt T. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. *Online J Curr Clin Trials* 1993. Doc No 110.
- [11] McDonnell M, Henderson DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. *J Paediatr Child Health* 1997;33(4):308–10.
- [12] Rabe H, Wacker A, Hülskamp G, Hörnig-Franz I, Schulze-Everding A, Harms E, Cirkel U, Louwen F, Witteler R, Schneider H. A randomized controlled trial of delayed cord clamping in very low birth weight preterm infants. *Eur J Pediatr* 2000;159(10):775–7.
- [13] Mercer J, McGrath M, Hensman A, Silverm H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. *J Perinatol* 2003;23(6):466–72.
- [14] Baenziger O, Stolkin F, Keel M, von Siebenthal K, Fauchere J, Das Kundu S, Dietz V, Bucher H, Wolf M. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. *Pediatrics* 2007;119(3):454–9.
- [15] Strauss R, Mock D, Johnson K, Cress G, Burmeister L, Zimmerman M, Bell E, Rijhsinghani A. A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. *Transfusion* 2008;48(4):658–65.
- [16] Ultee C, van der Deure J, Swart J, Lasham C, van Baar A. Delayed cord clamping in preterm infants delivered at 34–36 weeks' gestation: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008;93(1):F20–23.
- [17] Weckert R, Hancock H. The importance of delayed cord clamping for *Aboriginal babies: A life-enhancing advantage. *Women Birth* 2008;21(4):165–70.
- [18] Gokmen Z, Ozkiraz S, Tarcan A, Kozanoglu I, Ozcimen E, Ozbek N. Effects of delayed umbilical cord clamping on peripheral blood hematopoietic stem cells in premature neonates. *J Perinat Med* 2011;39:323–9.
- [19] Oh W, Fanaroff A, Carlo W, Donovan E, McDonald S, Poole W, of Child Health EKSNI, Network. HDNR. Effects of delayed cord clamping in very-low-birth-weight infants. *J Perinatol* 2011;31(Suppl):s68–71.
- [20] Hu X, Xu X. In: Hu X, Xu X, editors. The effects of different cord clamping time in preterm infants by vaginal delivery. Zhejiang University; 2015.
- [21] Ranjit T, Nesargi S, Rao PN, Sahoo JP, Ashok C, Chandrakala BS, Bhat S. Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. *Indian J Pediatr* 2015;82(1):29–34.
- [22] Salae R, Tanprasertkul C, Somprasit C, Bhamarapratana K, Suwannarurk K. Efficacy of delayed versus immediate cord clamping in late preterm newborns following normal labor: a randomized control trial. *J Med Assoc Thai* 2016;99(Suppl 4):S159–65.
- [23] Dong X, Sun X, Li M, Yu Z, Han S. Influence of delayed cord clamping on preterm infants with a gestational age of <32 weeks. *Zhongguo Dang Dai Er Ke Za Zhi* 2016;18:635–8, [in Chinese].
- [24] Backes C, Huang H, Iams J, Bauer J, Giannone P. Timing of umbilical cord clamping among infants born at 22 through 27 weeks' gestation. *J Perinatol* 2016;36:35–40.
- [25] Armanian A, Ghasemi Tehrani H, Ansari M, Ghaemi S. Is "delayed umbilical cord clamping" beneficial for premature newborns? *Int J Pediatr* 2017;5(5):4909–18.
- [26] Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: A randomized, controlled trial. *Pediatrics* 2006;117(4):1235–42.
- [27] Kugelmann A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R, Bader D. Immediate versus delayed umbilical cord clamping in premature neonates born <35 weeks: a prospective, randomized, controlled study. *Am J Perinatol* 2007;24(5):307–15.

- [28] Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, Evans N, Finlayson S, Fogarty M, Gebiski V, Ghadge A, Hague W, Isaacs D, Jeffery M, Keech A, Kluckow M, Popat H, Sebastian L, Aagaard K, Belfort M, Pammi M, Abdel-Latif M, Reynolds G, Ariff S, Sheikh L, Chen Y, Colditz P, Liley H,ritchard M, de Luca K, Forder P, Duley L, El-Naggar W, Gill A, Newnham J, Simmer K, Groom K, Weston P, Gullam J, Patel H, Koh G, Lui K, Marlow N, Morris S, Sehgal A, Wallace E, Soll R, Young L, Sweet D, Walker S, Watkins A, Wright I, Osborn D, Simes J. Delayed versus immediate cord clamping in preterm infants. *New Engl J Med* 2017;377(25):2245–455.
- [29] Duley L, Dorling J, Pushpa-Rajah A, Oddie S, Yoxall C, Schoonakker B, Bradshaw L, Mitchell E, Fawke J. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2017;103(1):F6–14.
- [30] Datta V, Kumar A, Yadav R. A randomized controlled trial to evaluate the role of brief delay in cord clamping in preterm neonates (34–36 weeks) on short-term neurobehavioral outcome. *J Trop Pediatr* 2017;63(6):418–24.
- [31] Rana A, Agarwal K. Safety of delayed umbilical cord clamping in preterm neonates less than 34 weeks gestation. *Indian J Pediatr* 2017;84(5):414.
- [32] Dipak N, Nanavati R, Kabra N, Srinivasan A, Ananthan A. Effect of delayed cord clamping on hematocrit, and thermal and hemodynamic stability in preterm neonates: a randomized controlled trial. *Indian Pediatr* 2017;54(2):112–5.
- [33] World Health Organization. Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. World Health Organization; 2014. Available from: http://www.who.int/nutrition/publications/guidelines/cord_clamping/en/. [Accessed 25 October 2023].
- [34] American Academy of Pediatrics and American Heart Association. Textbook of neonatal resuscitation. (8th ed.). American Academy of Pediatrics and American Heart Association; 2021. [Accessed 25 October 2023].
- [35] Haute Autorité de Santé. Transfusion de globules rouges homologues: produits, indications alternatives. Paris, France: Haute Autorité de Santé; 2014. Available from: [URL where the guidelines can be accessed, if available].
- [36] Queensland Clinical Guidelines. Normal birth. Brisbane, Australia: Queensland Health; 2017.
- [37] Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* (Online) 2012;8:CD003248.
- [38] Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: Systematic review and meta-analysis of controlled trials. *J Amer Med Assoc* 2007;297(11):1241–52.
- [39] McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2013;2013(7):CD004074.
- [40] McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2008;7(2):CD004074.
- [41] Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. *Cochrane Database Syst Rev* (Online) 2004;4(4):CD003248.
- [42] Chaparro CM, Neufeld LM, Tena Alavez G, Eguia-Líz Cedillo R, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. *Lancet* 2006;367(9527):1997–2004.
- [43] Correa S, Lonngi RG, Méndez CL, Padilla CT. Hacia un consenso sobre los criterios del tiempo oportuno para un adecuado pinzamiento del cordón umbilical. *UCIN* 2007;7(3):53–63.
- [44] Fogarty M, Osborn D, Askie L, Seidler A, Hunter K, Lui K, Simes J, Tarnow-Mordi W. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Amer J Obstet Gynecol* 2018;218(1):1–18.
- [45] Bruckner M, Katheria AC, Schmöler GM. Delayed cord clamping in healthy term infants: More harm or good? *Semin Fetal Neonatal Med* 2021;26(2):101221.
- [46] Boere I, Roest AA, Wallace E, Ten Harkel ADJ, Haak MC, Morley CJ, Hooper SB, Te Pas AB. Umbilical blood flow patterns directly after birth before delayed cord clamping. *Arch Dis Child Fetal Neonatal Ed* 2015;100(2):F121–5.
- [47] Downey CL, Bewley S. Historical perspectives on umbilical cord clamping and neonatal transition. *J R Soc Med* 2012;105(8):325–9.
- [48] Liyanage SK, et al. Guidelines on deferred cord clamping and cord milking: A systematic review. *Pediatrics* 2020;146(5):e20201429.
- [49] Mwakawanga DL, Mselle LT. Early or delayed umbilical cord clamping? Experiences and perceptions of nurse-midwives and obstetricians at a regional referral hospital in tanzania. *PLoS One* 2020;15(6):e0234854.
- [50] Peberdy L, Young J, Massey D, Kearney L. Integrated review of the knowledge, attitudes, and practices of maternity health care professionals concerning umbilical cord clamping. *Birth* 2022;49(4):595–615.
- [51] Gupta B, Yengkhom R, Banait N, Chetan C, Pareek P, Suryawanshi P. Hemodynamic parameters after delayed cord clamping (DCC) in term neonates: a prospective observational study. *BMC Pediatr* 2022;22(1):256.
- [52] Martín NR-C. Monitoreo sobre el tiempo de pinzado y corte de cordón umbilical. vigilancia de nuevas estrategias para la atención del parto. *Perinatol Reprod Humana* 2014;28(3):134–8.
- [53] Nesheli HM, Esmailzadeh S, Haghshenas M, Bijani Ali Moghaddam TG. Effect of late vs early clamping of the umbilical cord (on haemoglobin level) in full-term neonates. *J Pak Med Assoc* 2014;64(11):1303–5.
- [54] Andersson O, Hellström-Westas L, andersson D, Domellöf M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. *Br Med J* 2011;343(1):1–12.
- [55] Ceriani CJ. Pinzamiento precoz versus pinzamiento tardío del cordón umbilical en neonatos prematuros. Ginebra: La Biblioteca de Salud Reproductiva de la OMS; 2006.
- [56] Escarpa AM. Pinzamiento tardío vs pinzamiento precoz del cordón umbilical. *Reduca (Enferm Fisioter Podol)* 2012;4(5):242–70.
- [57] Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, te Pas AB, Morley CJ, Polglase GR, Hooper SB. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol* 2013;250(8):2113–26.
- [58] Polglase GR, Dawson JA, Kluckow M, Gill AW, Davis PG, te Pas AB, Crossley KJ, McDougall A, Wallace EM, Hooper SB. Ventilation onset prior to umbilical cord clamping (physiological-based cord clamping) improves systemic and cerebral oxygenation in preterm lambs. *PLoS One* 2015;591(8):2113–26.
- [59] Ježek F, Kulhánek T, Kalecký K, Kofránek J. Lumped models of the cardiovascular system of various complexity. *Biocybern Biomed Eng* 2017;37(4):666–78.
- [60] Son J, Du D, Du Y. Modelling and control of a failing heart managed by a left ventricular assist device. *Biocybern Biomed Eng* 2020;40(1):559–73.
- [61] Maciej K, Gianfranco F, Krzysztof Z, Krystyna G, Krzysztof J, P, Libera F, Arianna DM, Marek D. A hybrid (hydro-numerical) cardiovascular model: Application to investigate continuous-flow pump assistance effect. *Biocybern Biomed Eng* 2012;32(4):77–91.
- [62] Khan M, Vashisth S, Vijay R, Salhan AK. Computer based real time systems for analyzing cardiovascular response to orthostatic stress. *Biocybern Biomed Eng* 2015;35(4):232–9.
- [63] Siewnicka A, Janiszowski K, Pałko T, Wnuk P. Hybrid cardiovascular simulator as a tool for physical reproduction of the conditions prevailing in the apex of the heart. *Biocybern Biomed Eng* 2016;36(3):473–81.
- [64] Sepúlveda-Oviedo EH, Bermeo Clavijo LE, Méndez Córdoba LC. OpenModelica-based virtual simulator for the cardiovascular and respiratory physiology of a neonate. *J Med Eng Technol* 2022;46(3):179–97.
- [65] Chiara C, Elena C, Francesco M, Silvia S, Tain-Yen H, Giancarlo P. Mathematical modelling of the maternal cardiovascular system in the three stages of pregnancy. *Med Eng Phys* 2017;47:55–63.
- [66] Sepúlveda-Oviedo EH, Bermeo Clavijo LE, Méndez Córdoba LC. Desarrollo de una herramienta de simulación cardiovascular neonatal para la enseñanza y la investigación. In: XLVI congreso brasileiro de educação em engenharia (COBENGE) e no 1º simpósio internacional de educação em engenharia da ABENGE. 2018, p. 1–12.
- [67] Yigit MB, Kowalski WJ, Hutchon DJR, Pekkana K. Transition from fetal to neonatal circulation: Modeling the effect of umbilical cord clamping. *J Biomech* 2015;48(9):1662–70.
- [68] Goodwin J, van Meurs W, Sá-Couto C, Beneken J, Graves S. A model for educational simulation of infant cardiovascular physiology. *Anesth Analg* 2004;99(6):1655–64.
- [69] Sá-Couto C, andriessen P, Van Meurs W, Ayres-de Campos D, Sá-Couto P. A model for educational simulation of hemodynamic transitions at birth. *Pediatr Res* 2010;67(2):158–65.
- [70] Gordon J, Wilkerson W, Shaffer D, Armstrong E. “Practicing” medicine without risk: students’ and educators’ responses to high-fidelity patient simulation. *Acad Med: J Assoc Amer Med Coll* 2001;76(5):469–72.
- [71] Niermeyer S. Cardiopulmonary transition in the high altitude infant. *High Alt Med Biol* 2003;4(2):225–39.
- [72] Huikeshoven F, Coleman T, Jongasma H. Mathematical model of the fetal cardiovascular system: the uncontrolled case. *Am J Physiol* 1980;239(3):R317–25.
- [73] Pennati G, Bellotti M, Fumero R. Mathematical modeling of the human foetal cardiovascular system based on Doppler ultrasound data. *Med Eng Phys* 1997;19(4):327–35.
- [74] Fritzon P. Introduction to modeling and simulation of technical and physical systems. Londres: IEEE Press ed.; 2011.
- [75] Sepúlveda-Oviedo EH, Bermeo Clavijo LE, Méndez Córdoba LC. Supplementary material of the article “OpenModelica-based virtual simulator for the cardiovascular and respiratory physiology of a neonate”. Zenodo; 2023, p. 1–2.
- [76] Mateják M, Kulhánek T, Šilar J, Privitzer P, Ježek F, Kofránek J. Physiobrary - modelica library for physiology. In: Proceedings of the 10th international modelicaConference. Lund, Sweden; 2014, p. 499–505.
- [77] Mateják M, Kofránek J. Physiobrary - an integrative physiology in Modelica. In: Conf proc IEEE eng med biol soc. 2015, p. 1464–7.
- [78] Mateják M. In: Mateják M, editor. Physiobrary – modelica library for physiology. Physiobrary; 2023. Available from: <https://www.physiolibrary.org/>. [Accessed 18 October 2023].
- [79] Vilos G, Liggins G. Intrathoracic pressures in fetal sheep. *J Dev Physiol* 1982;4(4):247–56.

- [80] Hooper S, Wallace M. Role of the physicochemical environment in lung development. *Clin Exp Pharmacol Physiol* 2006;33(3):273–9.
- [81] Koch G. Alveolar ventilation, diffusing capacity and the A-a Po₂ difference in the newborn infant. *Respir Physiol* 1968;4(2):168–92.
- [82] Hoppensteadt FC, Peskin CS. Modeling and simulation in medicine and the life sciences. (2nd ed.). NewYork: Springer; 2002.
- [83] Sepúlveda-Oviedo EH, Bermeo Clavijo LE, Méndez Córdoba LC. Supplementary material of the article “Effect of timing of umbilical cord clamping and birth on fetal to neonatal transition: OpenModelica-based virtual simulator-based approach”. Zenodo; 2023, p. 4–6.
- [84] Kato M, Staub N. Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. *Circ Res* 1966;19:426–40.
- [85] Nagasawa H, Hamada C, Wakabayashi M, Nakagawa Y, Nomura S, Kohno Y. Time to spontaneous ductus arteriosus closure in full-term neonates. *Open Hear* 2016;3:e000413.
- [86] Rasanen J, Wood D, Weiner S, Ludomirski A, Huhta J. Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy. *Circulation* 1996;94(5):1068–73.
- [87] Migliavacca F, Dubini G, Pennati G, Pietrabissa R, Fumero R, Hsia T, de Leval M. Computational model of the fluid dynamics in systemic-to-pulmonary shunts. *J Biomech* 2000;33(5):549–57.
- [88] Guyton A. Textbook of medical physiology. (8th ed.). Philadelphia: W.B. Saunders Company; 1991.
- [89] Wang Y, Zhao S. Vascular biology of the placenta. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.
- [90] Khriesat W, Amarín Z, Kassab M, Shkour M, AL-Maghyreh M. Oxygen saturation immediately after birth in healthy full-term neonates born below sea level. *J Clin Neonatol* 2016;5:259–61.
- [91] Jackson B, Piasecki G, Novy M. Fetal responses to altered maternal oxygenation in rhesus monkey. *Amer J Physiol* 1987;252:R94–101.
- [92] Carter A. Placental oxygen transfer and the oxygen supply to the fetus. *Fetal Matern Med Rev* 1999;11:151–61.
- [93] McCullough R, Reeves J, Liljegren R. Fetal growth retardation and increased infant mortality at high altitude. *Arch Environ Health: Int J* 1977;32:36–9.
- [94] Lerner L. Physics for scientists and engineers. (2nd ed.). London: Jones and Bartlett Publishers; 1996.
- [95] Steven C, Nicola H. The alveolar gas equation. *Contin Educ Anaesth Crit Care Pain* 2004;4(1):24–7.
- [96] Rudolph A. Congenital diseases of the heart. (3rd ed.). San Francisco: Wiley-Blackwell; 2009.
- [97] Kakkilaya V, Pramanik AK, Ibrahim H, Hussein S. Effect of placental transfusion on the blood volume and clinical outcome of infants Born by cesarean section. *Clin Perinatol* 2008;35(3):561–70.
- [98] Ogata E, Kitterman J, Kleinberg F, Dong L, Willis M, Mates R. The effect of time of cord clamping and maternal blood pressure on placental transfusion with cesarean section. *Am J Obstet Gynecol* 1977;128:197–200.
- [99] Yao A, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. *Lancet* 1969;2(7626):871–3.
- [100] Yao A, Lind J. Effect of gravity on placental transfusion. *Lancet* 1969;2:505–8.
- [101] Philip A, Saigal S. When should we clamp the umbilical cord? *NeoReviews* 2004;5:e142–53.
- [102] Pluncevic J, Gontarev S, Dejanova B, Todorovska L, Shukova Stojmanovska D, Mancevska S. Red blood cell variables in children and adolescents regarding the age and sex. *Iran J Publ Health* 2019;48:704–12.
- [103] Lassila R, Weisel JW. Role of red blood cells in clinically relevant bleeding tendencies and complications. *J Thromb Haemost* 2023;21(11):3024–32.
- [104] Chou HG, Lee C. The theory of oxygen hemoglobin association. *Biosystems* 2023;229:104932.
- [105] Maharaj I, Gebrehiwot P, Dawson J, Blank D, Kamlin C, Manley B, Flemmer S, Davis P. The effect of cord clamping on oxygen saturation in infants immediately after birth. *J Paediatr Child Health* 2018;54(Suppl. 1):3–128.
- [106] Uslu S, Bulbul A, Can E, Zubarioglu U, Salihoglu O, Nuhoglu A. Relationship between oxygen saturation and umbilical cord pH immediately after birth. *Pediatr Neonatol* 2012;53(6):340–5.
- [107] Taşkın R, Kanbur A. The effect of delayed umbilical cord clamping on newborn's oxygen saturation and sucking success in primiparous pregnant. *J Obstet Gynaecol Res* 2022;Epub 2022. PMID: 36065164.
- [108] Kc A, Singhal N, Gautam J, Rana N, andersson O. Effect of early versus delayed cord clamping in neonate on heart rate, breathing and oxygen saturation during first 10 minutes of birth - randomized clinical trial. *Matern Health Neonatol Perinatol* 2019;30:5–7.
- [109] Ibrahim H, Krouskop R, Lewis D, Dhanireddy R. Placental transfusion: umbilical cord clamping and preterm infants. *J Perinatol* 2000;20:351–4.
- [110] Nelle M, Fisher S, Conze S, Beedgen B, Grischke E, Linderkamp O. Placental transfusion: umbilical cord clamping and preterm infants. *Pediatr Res* 1998;44:454.
- [111] Hofmeyr G, Bolton K, Bowen D, Govan J. Periventricular/intraventricular hemorrhage and umbilical cord clamping. Findings and hypothesis. *South Afr Med J* 1988;73(2):104–6.
- [112] Linderkamp O. Placental transfusion: determinants and effects. *Clin Perinatol* 1982;9:559–92.
- [113] Peltonen T. Placental transfusion: advantage and disadvantage. *Eur J Pediatr* 1981;137:141–6.
- [114] Arcilla RA, Oh W, Lind J, Gessner IH. Pulmonary arterial pressures of newborn infants born with early and late clamping of the cord. *Acta Paediatr Scand* 1966;55(3):305–15.
- [115] Yao AC, Lind J. Effect of gravity in placental transfusion. *Obstet Gynecol Surv* 1970;25(3):216–7.
- [116] Lu J, Yue G, Wang Q, Zhou X, Ju R. A review on development of placental transfusion in term and preterm infants. *Front Pediatr* 2022;10:890988.
- [117] Farrar D, Airey R, Law G, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: Weighing babies with cord intact. *BJOG: Int J Obstet Gynaecol* 2010;118:70–5.
- [118] Brouwer E, Knol R, Vernooij ASN, van den Akker T, Vlasman PE, Klumper FJCM, DeKoninck P, Polglase GR, Hooper SB, te Pas AB. Physiological-based cord clamping in preterm infants using a new purpose-built resuscitation table: a feasibility study. *Arch Dis Child - Fetal Neonatal Ed* 2018.
- [119] Knol R, Brouwer E, Vernooij A, Klumper F, DeKoninck P, Hooper S, Te pas A. Clinical aspects of incorporating cord clamping into stabilisation of preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2018;F1–5.
- [120] Badurdeen S, Davis PG, Hooper SB, Donath S, Santomartino GA, Heng A, Zannino D, Hoq M, Omar F Kamlin C, Kane SC, Woodward A, Roberts CT, Polglase GR, Blank DA, on behalf of the Baby Directed Umbilical Cord Clamping (BabyDUCC) collaborative group. Physiologically based cord clamping for infants $\geq 32+0$ weeks gestation: A randomised clinical trial and reference percentiles for heart rate and oxygen saturation for infants $\geq 35+0$ weeks gestation. *PLOS Med* 2022;19(6):1–20.
- [121] Knol R, Brouwer E, van den Akker T, DeKoninck PLJ, Lopriore E, Onland W, Vermeulen MJ, van den Akker-van Marle ME, van Bodegom-Vos L, de Boode WP, van Kaam AH, Reiss IKM, Polglase GR, Hutten GJ, Prins SA, Mulder EEM, Hulzebos CV, van Sambeek SJ, van der Putten ME, Zonnenberg IA, Hooper SB, Te Pas AB. Physiological-based cord clamping in very preterm infants: the aeration, breathing, clamping 3 (ABC3) trial-study protocol for a multicentre randomised controlled trial. *Trials* 2022;23(1):838.
- [122] Tan T, Sepulveda W. Acardiac twin: a systematic review of minimally invasive treatment modalities. *Ultrasound Obstet Gynecol* 2003;22(4):409–19.
- [123] Ashish KC, Singhal N, Gautam J, Rana N, Andersson O. Effect of early versus delayed cord clamping in neonate on heart rate, breathing and oxygen saturation during first 10 minutes of birth -randomized clinical trial. *Matern Health Neonatol Perinatol* 2019;5.
- [124] Valero WR, Zirena IH, Bejar MC, Dueñas JR. Adaptation period characteristics in high - altitude newborn. *Acta Méd Peruana* 2009;26(3):151–5.
- [125] Gonzales G, Salirrosas A. Arterial oxygen saturation in healthy newborns delivered at term in cerro de pasco (4340 m) and lima (150 m). *Reprod Biol Endocrinol: RBE* 2005;3:46.
- [126] Rudolph A. Fetal and neonatal pulmonary circulation. *Annu Rev Physiol* 1979;41:383–95.
- [127] Emmanouilides G, Moss A, Monset-Couchard M, Marcano B, Rzeznick B. Cardiac output in newborn infants. *Biol Neonate* 1970;15(34):186–97.
- [128] Kang C, Enfa Z, Zhou Y, Zhao H, Liu Y, Gao N, Huang X, Liu B. Dynamic changes of pulmonary arterial pressure and ductus arteriosus in human newborns from birth to 72 hours of age. *Medicine* 2016;95:e2599.
- [129] Bennet L, Roelfsema V, George S, Dean JM, Emerald BS, Gunn AJ. The effect of cerebral hypothermia on white and grey matter injury induced by severe hypoxia in preterm fetal sheep. *J Physiol (London)* 2007;578(2):491–506.
- [130] Beall CM. Two routes to functional adaptation: Tibetan and andean high-altitude natives. *Proc Natl Acad Sci* 2007;104(suppl_1):8655–60.
- [131] Llanos AJ, Ebensperger G, Herrera EA, Reyes RV, Pulgar VM, Serón-Ferré M, Díaz M, Parer JT, Giussani DA, Moraga FA, Riquelme RA. Fetal and postnatal pulmonary circulation in the alto andino. *Placenta* 2011;32:S100 – S103.
- [132] Gonzales GF. Impact of high altitude on pregnancy and newborn parameters. *Rev Peruana Med Exp Salud Públ* 2012;29(2):242–9.
- [133] Yan J, Ren J, Zhang J, Li J, Zhang X, Ma Y, Gao L. The short and long term consequences of delayed cord clamping on late pre-term infants. *Int J Womens Health* 2023;15:361–8.
- [134] Mercer J, Erickson-Owens D, Collins J, Barcelos M, Parker A, Padbury J. Effects of delayed cord clamping on residual placental blood volume, hemoglobin and bilirubin levels in term infants: A randomized controlled trial. *J Perinatol* 2016;37:260–4.
- [135] Ranjit T, Nesargi S, Rao P, Sahoo J, Ashok C, Chandrakala B, Bhat S. Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. *Int J Women's Health* 2015;82(1):29–34.
- [136] Wilander M, Sandblom J, Thies-Lagergren L, andersson O, Svedenkrans J. Bilirubin levels in neonates ≥ 35 weeks of gestation receiving delayed cord clamping for an extended time—An observational study. *J Pediatr* 2023;257:113326.
- [137] Winkler A, Isacson M, Gustafsson A, Svedenkrans J, andersson O. Cord clamping beyond 3 minutes: Neonatal short-term outcomes and maternal postpartum hemorrhage. *Birth* 2022;49(4):783–91.

- [138] Shao H, Gao S, Lu Q, Zhao X, Hua Y, Wang X. Effects of delayed cord clamping on neonatal jaundice, phototherapy and early hematological status in term cesarean section. *Ital J Pediatr* 2021;47.
- [139] Sepúlveda-Oviedo EH, Bermeo L, Méndez-Córdoba LC. Explanation of the PatientEvoPhysio library. *Zenodo* 2023;1:1–11.
- [140] Sepúlveda-Oviedo EH, Travé-Massuyès L, Subías A, Pavlov M, Alonso C. Fault diagnosis of photovoltaic systems using artificial intelligence: A bibliometric approach. *Heliyon* 2023;9(11):e21491.
- [141] Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32(4):260–7.
- [142] Niermeyer S, Velaphi S. Promoting physiologic transition at birth: Re-examining resuscitation and the timing of cord clamping. *Semin Fetal Neonatal Med* 2013;18(6):385–92.
- [143] Sepúlveda-Oviedo EH, Bermeo Clavijo LE, Méndez Córdoba LC. Modelo del procedimiento de adaptación de neonatal inmediata: una aplicación de sistemas de eventos discretos en neonatología. In: XXII congreso brasileiro de automática. 2018, p. 1–9.
- [144] Asfour V, Bewley S. Cord clamping practice could affect the ratio of placental weight to birthweight and perinatal outcomes. *BJOG: Int J Obstet Gynaecol* 2011;118(12):1539–40.
- [145] Sepúlveda-Oviedo EH. Estudio de la práctica del pinzamiento del cordón umbilical usando análisis computacional de la información bibliográfica, modelos de eventos discretos y modelos dinámicos (Diploma thesis), Universidad Nacional de Colombia; 2019.
- [146] Vain N, Satragno D, Gorenstein A, Gordillo J, Berazategui J, Alda M, et al. Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial. *Lancet* 2014;384:235–40.
- [147] Mercer JS, Erickson-Owens DA. Rethinking placental transfusion and cord clamping issues. *J Perinatal Neonatal Nurs* 2012;26(3):202–17.