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Transition from fetal to neonatal circulation: Modeling the effect of umbilical cord clamping

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ABSTRACT

Hemodynamics of the fetal to neonatal transition are orchestrated through complex physiological changes and results in cardiovascular adaptation to the adult biventricular circulation. Clinical practice during this critical period can influence vital organ physiology for normal newborns, premature babies and congenital heart defect patients. Particularly, the timing of the cord clamping procedure, immediate (ICC) *vs.* delayed cord clamping (DCC), is hypothesized to be an important factor for the *transitory fetal hemodynamics*. The clinical need for a quantitative understanding of this physiology motivated the development of a lumped parameter model (LPM) of the fetal cardio-respiratory system covering the late-gestation to neonatal period. The LPM was validated with *in vivo* clinical data and then used to predict the effects of cord clamping procedures on hemodynamics and vital gases. Clinical time-dependent resistance functions to simulate the vascular changes were introduced. For DCC, placental transfusion (31.3 ml) increased neonatal blood volume by 11.7%. This increased blood volume is reflected in an increase in preload pressures by ~20% compared to ICC, which in turn increased the cardiac output (CO) by 20% (CO_{ICC}=993 ml/min; CO_{DCC}=1197 ml/min). Our model accurately predicted dynamic flow patterns *in vivo*. DCC was shown to maintain oxygenation if the onset of pulmonary respiration was delayed or impaired. On the other hand, a significant 25% decrease in oxygen saturations was observed when applying ICC under the same physiological conditions. We conclude that DCC has a significant impact on newborn hemodynamics, mainly because of the improved blood volume and the sustained placental respiration.

1. Introduction

Circulatory physiology of the newborn goes through complex transitions in order to shift the respiratory function from the placenta to the lungs, characterized by the closure of fetal shunts, expansion of the lungs, and removal of placental circulation (Friedman and Fahey, 1993; Rudolph, 1970). In order to speed up and manage the fetal-to-neonatal transition, immediate cord clamping (ICC) has been adopted as a standard clinical practice. However, this practice has been challenged, as recent findings demonstrated that delaying the cord clamping (DCC) for at least 30–60 s can be beneficial for the neonate, especially for the preterm due to the transfusion of placental resources (ACOG's Committee on Obstetric Practice, 2012; Hutchon, 2013; Raju, 2013), however it is possible to increase the net effect of transfusion by prolonging the timing of DCC considering that umbilical flow persists as long as 5 to 10 min after birth (Boere et al., 2015; Usher et al., 1963). Recent *in vivo* studies in preterm lambs indicated that DCC improves cardiovascular function through improved hemodynamic stability and increased cardiac output (CO) during the first 30 min after cord clamping (Bhatt et al., 2013). In preterm infants, both superior vena cava return and right ventricle output (RVO) were higher for the DCC group compared to the ICC over the critical first 2 days of life (Sommers et al., 2012). These observations strengthen the view that ICC can lead to reduced cardiovascular function due to hypovolemia and irregular neonatal hemodynamics (Hutchon, 2013).

ICC is also associated with lower peripheral oxygen saturation at birth (Smit et al., 2014). Prediction of fundamental vasoactive gases in relation to the cord clamping procedures is essential as placental flow is associated with the expansion of the lungs and remodeling of fetal shunts as it carries important vasoactive agents such as oxygen and prostaglandins PGE_2 (Coceani and Olley, 1973; Friedman and Fahey, 1993; Hutchon, 2013). Therefore, ICC has the likelihood of altering the fetal transition through multiple pathways where the hemodynamic and respiratory components can be

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dissected. Models and quantitative information of the early neonatal circulation and the effects of cord clamping are particularly required for the investigation of new management strategies during neonatal resuscitation (Niermeyer and Velaphi, 2013) and devices (Hutchon, 2013).

Our aims in this study are to 1) construct a physiologically accurate and detailed lumped parameter model (LPM) of the transition from fetal-to-neonatal circulation at birth and 2) investigate and compare the two cord clamping scenarios, namely DCC and ICC, based on their relative impacts on hemodynamics and respiration in the transitioning circulation of a term infant. In our simulations, we adopted a prolonged DCC case in order to observe the full effect of placental transfusion on the newborn, in which the clamp is applied after the umbilical flow completely ceases due to physiological constriction of umbilical arteries. ICC is simulated as standard in which clamp is applied at the beginning of transition.

To our knowledge, a *system-level* hemodynamic investigation of the *continuous* transition from fetal-to-neonatal circulation in the human has not been undertaken except for a simplified representation without gas exchange, whilst isolated lumped parameter studies of the fetal circulation at late gestation are available in the literature (Huikeshoven et al., 1985; Pennati et al., 1997; Pennati and Fumero, 2000; Sa-Couto et al., 2010). We believe that the present model would be important for neonatologists in understanding the fetal transition in detail and to improve clinical interventions with the transitioning fetal circulation. In the following sections, we use the abbreviations defined in Fig. 1 to refer to the LPM organ compartments and vessels. This format was chosen in order to avoid excessive in-text explanations of acronyms. A list of abbreviations is also given in Table 1.

2. Methods

2.1. Hemodynamic model

Using our neonatal and pediatric circulatory LPM framework (Pekkan et al., 2005; Peskin and Tu, 1986; Sundareswaran et al., 2008), we constructed a representative fetal circuit (Fig. 1) inspired from an earlier design by Pennati et al. (Pennati et al., 1997). Compliance (C) chambers were used to model major

Table 1
List of abbreviations.

Table of abbreviations			
ICC	Immediate cord clamping	R	Resistance
DCC	Delayed cord clamping	C	Compliance
LPM	Lumped parameter model	τ	Transition time
CO	Cardiac output	r	Ventilation–perfusion ratio
CCO	Combined cardiac output	EF	Ejection fraction of the ventricle
SO_2	Oxygen saturation	LVO	Left ventricular output
$[O_2]$	Oxygen concentration	RVO	Right ventricular output
PO_2	Partial pressure of oxygen	LV	Left ventricle
Q	Flow rate	RV	Right ventricle
P	Pressure	DA	Ductus arteriosus
V	Volume		

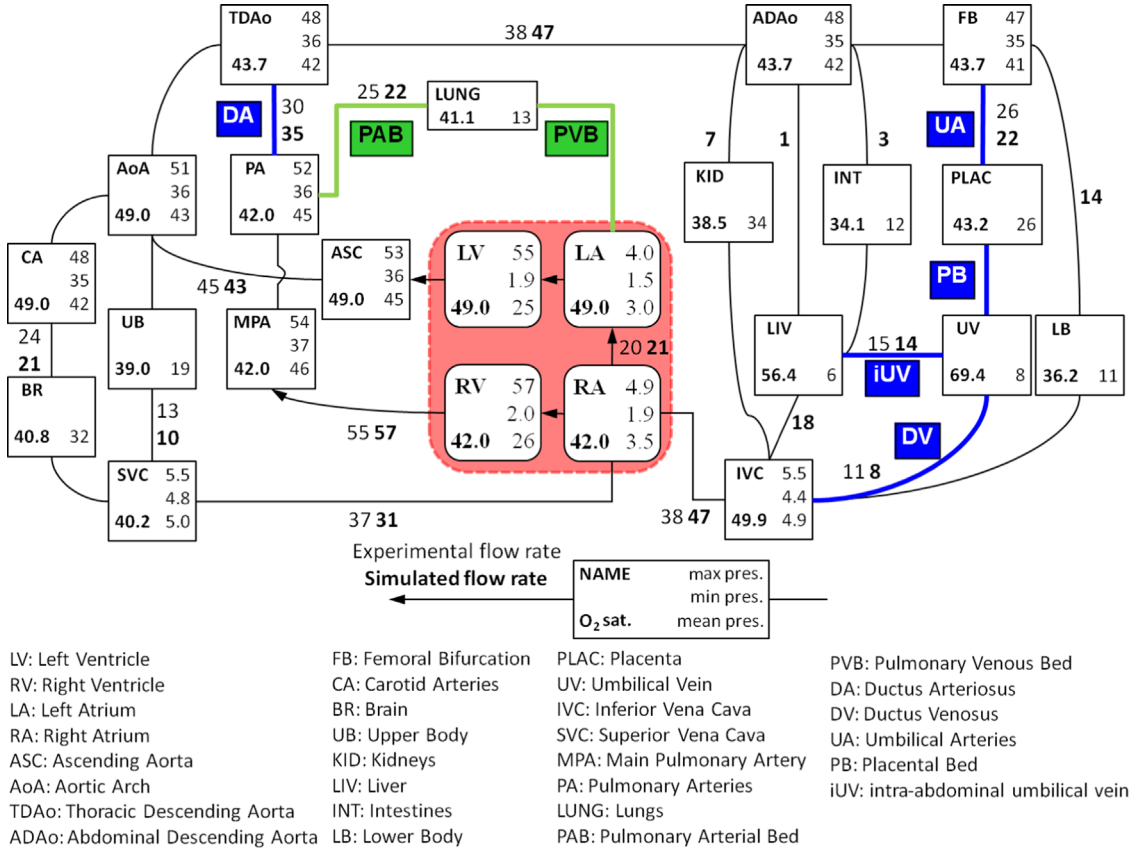

Fig. 1. Network schematics of the transitionary fetal cardiovascular circuit. Connecting lines represent arterial, capillary and venous resistance elements, and compartments correspond to compliance chambers. Arrows describe the direction of trans-valvular flow. Cycle-averaged flow rate distributions as a percentage of combined cardiac output (%CCO) is labeled on the connecting vessels (CCO=1.5 l/min), simulated flow rates are displayed in bold, experimental *in vivo* flow rates are selected values that were obtained from the literature (Kiserud et al., 2006; Mielke and Benda, 2001; Molina et al., 2008; Rasanen et al., 1996; Rudolph, 2009). Minimum–maximum-mean pressures (mmHg), and oxygen saturations (SO_2%) as well as the names of the compartments are displayed in boxes. All values correspond to the fetal circulation just before birth at the late-gestation period. *Blue* colored vessels represent the connections that close and *green* color represents connections that open during the fetal-to-neonatal transition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)