



# Maturation of Intestinal Oxygenation: A Review of Mechanisms and Clinical Implications for Preterm Neonates

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Nutrient requirements of preterm neonates may be substantial, to support growth and maturation processes in the presence of challenging post-natal circumstances. This may be accompanied by substantial intestinal oxygen requirements. Preterm neonates may not be able to meet these oxygen requirements, due to a developmental delay in intestinal oxygenation regulation mechanisms. This review summarizes the available literature on post-natal maturation of intestinal oxygenation mechanisms and translates these changes into clinical observations and potential implications for preterm neonates. The different mechanisms that may be involved in regulation of intestinal oxygenation, regardless of post-natal age, are first discussed. The contribution of these mechanisms to intestinal oxygenation regulation is then evaluated in newborn and mature intestine. Finally, the course of clinical observations is used to translate these findings to potential implications for preterm neonates.

**Keywords:** newborn, preterm neonates, intestinal circulation, intestinal oxygenation, near-infrared spectroscopy, growth and development

## INTRODUCTION

The major functions of the intestine are immunological and digestion-absorption (1, 2). The immunological function includes a wide variety of cells and strategies, beyond the scope of this review, and among other things prevents bacterial translocation across the epithelium in the presence of microbial colonization of the gut (1, 3, 4). The digestive-absorptive function includes production of digestive enzymes and absorption of carbohydrates, lipids, proteins, and vitamins (2). Ultimately, the intestine provides required nutrients to support body growth and function. The nutrient requirements of neonates may be substantial, consequent to maturation processes and tissue growth (5, 6). In preterm neonates, these nutritional requirements may be even greater, due to challenging post-natal circumstances, e.g., infection and respiratory distress (7). To meet ongoing nutritional demands, sufficient intestinal oxygenation is essential for intestinal function (8).

After birth, the intestine transitions from a relatively dormant organ to the sole site for nutrient absorption, thus requiring a concomitant increase in oxygen supply (9). This transition is accompanied by rapid tissue growth relative to the whole body, as the intestine increases its weight by 40–70% within 24 h and 4-fold within 10 days (10). Additionally, the change from continuously swallowing amniotic fluid to tolerating intermittent enteral feeds may alter intestinal physiology

(11). Therefore, the intestine and its associated circulation are subject to a considerable fetal-to-neonatal adaptation which continues to mature during early life (9, 11). Although little is known about post-natal changes in the intestinal circulation of preterm neonates, it can be speculated that these occur with increasing gestational age and post-natal age, as was recently described for the cerebral circulation (12). Among other factors, this may predispose preterm neonates to gastrointestinal complications, such as feeding issues, necrotizing enterocolitis (NEC), and poor growth (13–15).

Monitoring of intestinal oxygenation may facilitate early identification of gastrointestinal complications. Intestinal blood flow velocity can be measured using Doppler, but this provides only momentary information on oxygen delivery and not oxygen consumption (16). Near-infrared spectroscopy (NIRS) is a non-invasive, bedside technique used to continuously monitor regional oxygen saturation ( $rSO_2$ ) (17). Previous studies have reported promising results for splanchnic  $rSO_2$  ( $r_sSO_2$ )-monitoring for detecting hemodynamic changes that accompany physiologic and pathophysiologic conditions (18, 19). Currently, the use of splanchnic NIRS remains mostly limited to research settings. A better understanding of the different mechanisms regulating intestinal oxygenation may facilitate interpretation of  $r_sSO_2$  and advance clinical applications of  $r_sSO_2$ -monitoring.

In this review, we will first discuss the presumed mechanisms regulating intestinal oxygenation regardless of post-natal age, derived primarily from animal models. Next, we will discuss maturation of these mechanisms and elaborate on potential clinical implications for preterm neonates.

## OVERVIEW OF MECHANISMS REGULATING INTESTINAL OXYGENATION

Intestinal oxygenation represents the balance between oxygen supply and oxygen demand. Intestinal oxygen supply can be divided into convective delivery, from mesenteric arteries to intestinal capillaries, and diffusive delivery, from intestinal capillaries to parenchymal cells (20). Convective delivery depends on intestinal blood flow and arterial oxygen content and is modulated by resistance vessels, i.e., terminal mesenteric and submucosal arterioles (20, 21). In contrast, diffusive delivery depends on functional capillary density and capillary-to-cell local  $PO_2$  gradients, and is modulated by precapillary sphincters (20, 21).

Intestinal oxygenation is regulated at both local and systemic levels (21, 22). Local mechanisms provide real-time modulation of intestinal oxygenation and reflect an intestinal intrinsic capacity (21, 23). Systemic, or extrinsic, mechanisms integrate intestinal circulation into the systemic circulation (22). In the next sections, we will discuss these mechanisms in more detail. These mechanisms are summarized in **Figure 1**.

### Intrinsic Regulation of Intestinal Oxygenation

Intrinsic mechanisms for regulating intestinal oxygenation are divided into myogenic factors, metabolic factors, and endothelial

vasoactive compounds (24). Both myogenic and metabolic factors participate in pressure-flow autoregulation, i.e., the ability to maintain vascular flow during changes in perfusion pressure. However, the contribution of metabolic factors to this phenomenon seem to exceed those of myogenic factors (25). Additionally, overall vascular responses may be modified by endothelial vasoactive compounds (26).

The myogenic mechanism aims to sustain capillary pressure and transcapillary fluid exchange during changes in transmural pressure (23, 27). Increases in intravascular pressure lead to vasoconstriction in resistance vessels and closure of precapillary sphincters (28). Myogenic vasoconstriction in response to circumferential stretch of vascular smooth muscle is mediated by  $Ca^{2+}$  influx,  $Ca^{2+}$  release from the sarcoplasmic reticulum, and increased  $Ca^{2+}$ -sensitivity of contractile myofilaments (29). Intracellular signaling pathways leading to these events may involve protein kinase C (30).

The metabolic mechanism aims to sustain blood flow and oxygen delivery during changes in tissue metabolism (23). Increases in tissue metabolism leads to vasodilation of resistance vessels and relaxation of precapillary sphincters, by reduction of tissue  $PO_2$  and interstitial accumulation of vasoactive metabolites, such as  $H^+$ ,  $K^+$ , and adenosine (23). Moderate increases in tissue metabolism seem to be associated with augmented diffusive oxygen delivery, whereas greater increases in tissue metabolism seem to be supported by augmentation of convective oxygen delivery (31).

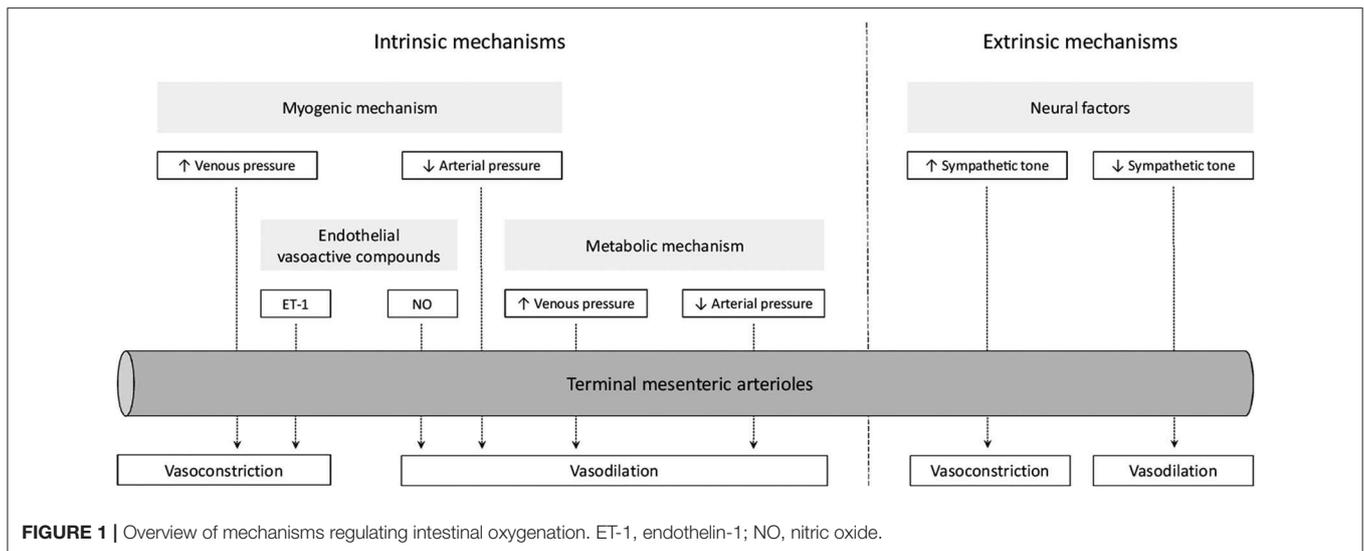
Endothelial vasoactive compounds modulate vascular resistance during changes in shear stress generated by blood flow against the static endothelium (26). The principal relaxing factor is nitric oxide (NO) (32–34). The principal constricting factor is endothelin-1 (ET-1) (35). Although activation of both  $ET_A$ - and  $ET_B$ -receptors on smooth muscle cells leads to vasoconstriction, activation of  $ET_B$ -receptors on endothelial cells leads to NO-mediated vasodilation (35).

It has been suggested that the enteric nervous system participates in regulation of intestinal oxygenation, however, as this seems to be mediated via endothelial release of nitric oxide (NO), this will not be discussed separately (36). A direct effect of gastrointestinal hormones and peptides in the regulation of intestinal oxygenation has not been clearly established and will therefore not be further addressed in this review (23).

### Extrinsic Regulation of Intestinal Oxygenation

Extrinsic mechanisms include neural factors and circulating vasoactive compounds (22). The physiological role of these compounds, including norepinephrine, angiotensin II, vasopressin, histamine, and bradykinin, is uncertain, as these were mostly studied using exogenous administration (23).

Splanchnic nerve stimulation produces a pattern of changes in the intestinal vasculature that is characterized by three phases: a constrictor phase, an escape phase, and a hyperemic phase (23). First, nerve stimulation leads to constriction of resistance vessels and closure of precapillary sphincters. However, during continued sympathetic stimulation, blood flow



partially recovers. It is suggested that accumulation of local metabolites and/or release of vasodilators from sensory nerves causes this autoregulatory escape by relaxation of previously constricted resistance vessels (37). Cessation of sympathetic stimulation is followed by a hyperemic phase before blood flow gradually returns to baseline (38). This post-stimulatory hyperemia may be explained by vasodilator metabolite release during the escape phase (39).

The intestine is extensively innervated by parasympathetic fibers originating from the vagus nerve. Although these fibers may have an indirect effect on intestinal oxygenation via changes in intestinal motility and secretion, there does not appear to be a direct vasoactive effect (23).

Several reviews on post-natal maturation of these intrinsic and extrinsic mechanisms describe that some may not be functionally mature at birth, whereas others may functionally decline in the post-natal period (9, 40–44). However, these reviews do not provide guidance for clinical practice, specifically with regard to preterm neonates. Therefore, our aim was to review the literature on maturation of intestinal oxygenation mechanisms and translate these changes into clinical observations with potential implications for preterm neonates.

## METHODS

A literature search was conducted to evaluate reports on the post-natal maturation of intestinal oxygenation mechanisms in neonates. The search strategy is presented in **Table 1**. English-language articles were selected only if they included a comparison between newborn and mature intestinal oxygenation. Furthermore, as we were mostly interested in baseline intestinal hemodynamics, we excluded articles in which external influences or interventions were investigated. In addition to the database search, we screened the reference lists of all relevant articles for additional publications. To identify clinical studies in preterm neonates, the search strategy

was repeated, following the same stepwise procedure, with several additional search terms, as presented in **Table 1**. We excluded articles that included only sick infants or studied the effect of external influences. In case a control group was included, we included the article, but only present results for the control group.

## RESULTS

Our initial search resulted in 9,837 articles. We assessed titles and abstracts of all articles, of which 114 appeared relevant. One additional publication was ascertained using the reference lists within these articles. After reading the full texts, 27 articles were included in this review (**Figure 2A**). The main findings are presented in **Table 2**.

### Postnatal Maturation of Mechanisms Regulating Intestinal Oxygenation

In the neonatal intestine, basal vascular resistance seems to be determined by myogenic factors, endothelial vasoactive compounds, and neural factors, based on observations in newborn swine (45, 51, 55, 58, 61, 66, 67). Using a swine model, Nowicki et al. (46) demonstrated in several studies that pressure-flow autoregulation is absent in neonatal intestine (54). Therefore, decreases in arterial pressure result in decreased intestinal blood flow. Moreover, these studies indicate that subsequent increases in oxygen extraction are insufficient to meet intestinal oxygen demand (48, 50, 53). The absence of pressure-flow autoregulation may indicate immaturity of the myogenic and/or metabolic mechanisms described above. However, myogenic vasoconstriction has been observed in newborn swine in response to increases in venous pressure (45, 47, 54, 58, 62). Therefore, it seems more likely that the absence of pressure-flow autoregulation reflects immaturity of the metabolic mechanism. Neonatal intestine may thus lack an important vasodilator mechanism.

**TABLE 1** | Search strategy.

#	Searches	Results
<b>Postnatal maturation of intestinal oxygenation mechanisms</b>		
1	Intestine, small [mh]	160,222
2	Splanchnic circulation/physiology [mh]	2,523
3	Intestine, small/blood supply* [mh]	6,624
4	Intestine, small/physiology [mh]	52,907
5	Mesenteric arteries [mh]	16,536
6	Splanchnic [tiab]	9,642
7	Abdom* [tiab]	344,335
8	Intestin* [tiab]	361,977
9	Mesenter* [tiab]	59,868
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	815,899
11	Hemodynamics/physiology [mh]	153,990
12	Vascular resistance/physiology [mh]	7,376
13	Vasoconstriction/physiology [mh]	6,745
14	Vasodilation/physiology [mh]	10,143
15	Hemodynamics [tiab]	48,463
16	Vascular resistance [tiab]	31,064
17	Vasoconstrict* [tiab]	42,933
18	Vasodilat* [tiab]	67,236
19	Perfusion [tiab]	159,441
20	Circulat* [tiab]	403,596
21	Blood flow [tiab]	167,197
22	Oxygenation [tiab]	51,192
23	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	924,027
24	#10 AND #23	49,658
25	Infant, Newborn [mh]	600,550
26	Infant [tiab]	216,859
27	Newborn [tiab]	137,450
28	Neonat* [tiab]	263,693
29	Post-natal [tiab]	103,008
30	Develop* [tiab]	4,280,256
31	#25 OR #26 OR #27 OR #28 OR #29 OR #30	5,003,395
32	#24 AND #31	9,837
<b>Clinical observations</b>		
33	Ultrasonography [mh]	70,985
34	Doppler [tiab]	102,865
35	Spectroscopy, Near-Infrared [mh]	13,026
36	Near-infrared spectroscopy [tiab]	11,392
37	#33 OR #34 OR #35 OR #36	490,849
38	#32 AND #37	330
39	Preterm [tiab]	67,490
40	#38 AND #39	145

#, search number; \*, truncation; mh, MeSH term; tiab, title or abstract

Moreover, there may be a greater amount of constricting factors, as demonstrated by a greater quantity of ET<sub>A</sub>- and ET<sub>B</sub>-receptors in newborn swine compared to mature swine (59, 63). In the presence of these vasoconstrictor influences, i.e., the

myogenic mechanism and ET-1, there seems to be an important role for NO as a vasodilator to maintain intestinal oxygenation in neonates. This assumption is supported by findings of Reber et al. (60, 61) who demonstrated that NO production is considerably greater in newborn swine compared with mature swine under both basal and stimulated conditions.

In mature intestine, basal vascular resistance seems to be determined by passive-elastic characteristics of the vasculature rather than active constrictor or dilator tone, based on observations in mature swine (42, 46, 53). Pressure-flow autoregulation is present in mature swine and seems to be associated with venous PO<sub>2</sub>, consistent with the metabolic mechanism described above (46, 48–50, 53, 54). Therefore, during decreases in arterial pressure, blood flow is still maintained in mature swine compared to newborn swine and concomitant increases in oxygen extraction may enable mature intestine to more consistently meet oxygen demand (46, 48–50, 53, 54). In contrast to newborn swine, myogenic vasoconstriction in response to venous pressure elevation seems to be absent in mature swine (47, 54, 58, 62). As the influence of vasoconstrictor forces, i.e., the myogenic mechanism and ET-1, decreases with advancing post-natal age, it follows that mature intestine may not require the same vasodilator forces as neonatal intestine. Indeed, several studies showed that NO production and the degree of flow-induced vasodilation are considerably smaller in mature swine than in newborn swine (51, 54, 60, 61).

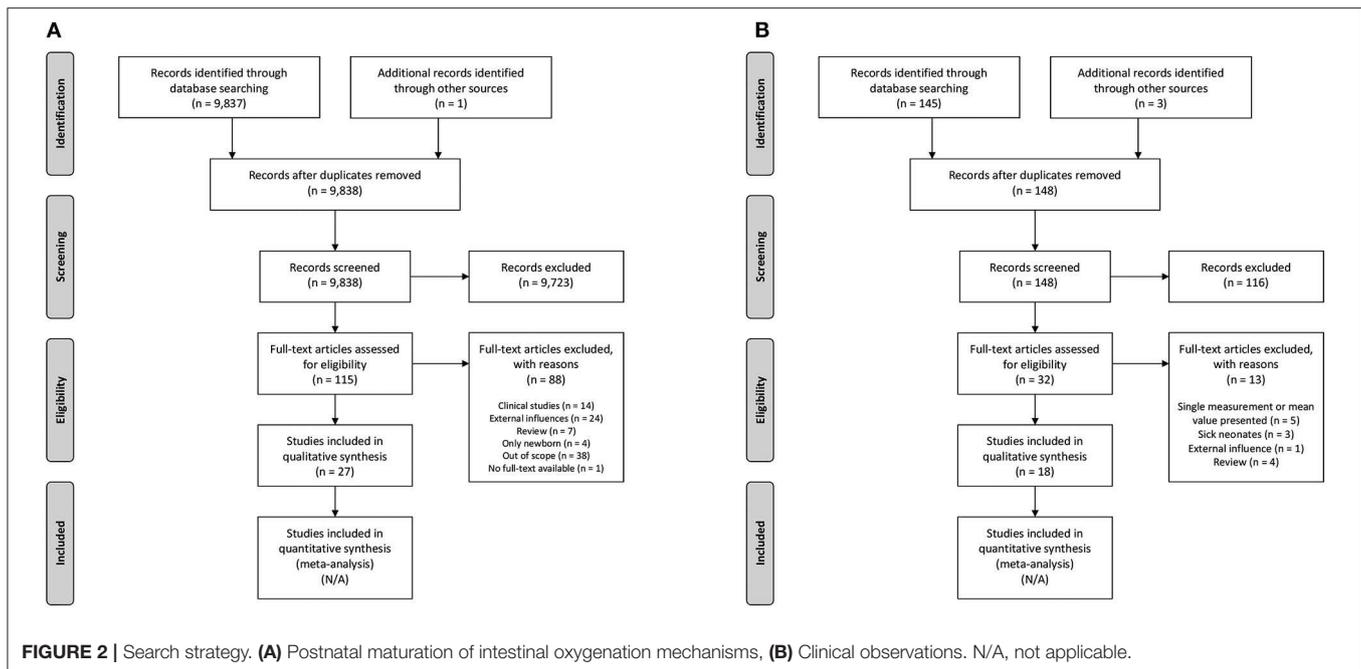
In conclusion, during post-natal maturation, the contribution of the metabolic mechanism in regulation of intestinal oxygenation increases, whereas the influences of the myogenic mechanism and endothelial vasoactive compounds decrease. In neonatal intestine, pressure-flow autoregulation is not yet functional, possibly due to immaturity of the metabolic mechanism.

## Translation to Clinical Observations

To the best of our knowledge, there are no studies available that investigate post-natal maturation of intestinal oxygenation mechanisms in preterm intestine, nor studies that compared maturation of intestinal oxygenation mechanisms between preterm and term intestine.

Therefore, we used the clinical studies that were identified by the additional search strategy to translate the results into clinical observations for preterm neonates. Our additional search resulted in 145 articles. We assessed titles and abstracts of all articles, of which 29 appeared relevant. Three additional publications were ascertained using the reference lists within these articles. After reading the full texts, 18 articles were included in this review (**Figure 2B**). The main findings are presented in **Table 3**.

In preterm neonates, intestinal perfusion increases in early life, as demonstrated by increases in peak systolic flow (PSV) and time-averaged mean velocity (TAMV), measured with Doppler, until day 28 of life (73–79, 81). Despite increases in blood flow during the first weeks of life, splanchnic oxygen saturation (r<sub>s</sub>SO<sub>2</sub>), estimated using near-infrared spectroscopy (NIRS), initially decreases in the first week of life and then increases until day 21 after birth (83, 84, 86–88). Advancing gestational age



(GA) is associated with both higher blood flow and higher  $r_s\text{SO}_2$  (78, 80, 84).

## INTERPRETATION AND DISCUSSION

Our review of the literature shows that pressure-flow autoregulation is only present in mature intestine, as demonstrated in animal studies. In contrast, neonatal intestine relies on increases in oxygen extraction to meet oxygen demand during decreases in arterial pressure. Clinical observations demonstrate lower baseline hemodynamic and oxygenation characteristics in preterm compared to term neonates. These results suggest a developmental delay of vasodilator forces and a smaller reserve to increase intestinal oxygen extraction in preterm neonates that may endanger intestinal oxygenation during decreases in arterial pressure.

Oxygen requirements of neonatal intestine, and specifically those of preterm neonatal intestine, may be substantial, due to a high nutritional demand to support growth and maturation processes (7). Our review of the literature shows that preterm neonates may not be able to meet these requirements, as pressure-flow autoregulation is still absent and increases in oxygen extraction are insufficient to meet tissue oxygen demand (46, 48–50, 53, 54). Clinical studies showed that  $r_s\text{SO}_2$  initially decreases after birth, possibly indicating that oxygen extraction is already maximized under basal conditions (83, 84, 86, 87). Although the course of intestinal blood flow and  $r_s\text{SO}_2$  in early post-natal life has not been studied with simultaneous Doppler and NIRS measurements, the initial decrease in  $r_s\text{SO}_2$  suggests that the increase in oxygen extraction is greater than the increase in blood flow during the first days of life. We hypothesize that this could be due to patency of the ductus arteriosus. This hypothesis is supported by findings of Ledo et al. (87) who investigated the effect of ductal patency on the course of  $r_s\text{SO}_2$  in preterm

neonates and found that the increases in  $r_s\text{SO}_2$  from day 3 of life are paralleled by ductal closure. The initial decrease in  $r_s\text{SO}_2$  may thus be explained by ductal steal, resulting in reduced diastolic flow in the descending aorta, resulting in a decreased intestinal perfusion pressure, and in the absence of intestinal pressure-flow regulation, preterm intestine relies on increases in oxygen extraction (73, 74, 80, 82, 87). This may enable preterm neonates to meet intestinal oxygen requirements during baseline conditions, yet creates unfavorable conditions during periods of additional stress. A recent review by Chaaban et al. (44) showed that the predominant response of neonatal intestine to decreases in oxygen delivery or increases in oxygen demand is increased oxygen extraction. In preterm neonates, however, it may not be possible to further increase oxygen extraction. Therefore, during periods of additional oxygen requirements, preterm neonates may fail to meet intestinal oxygen requirements, leading to disruption of the intestinal barrier and reduced nutrient absorption.

There may be an important role for NO to facilitate oxygen delivery in neonatal intestine during baseline conditions. Our review of the literature demonstrates that NO counteracts active vasoconstrictor tone, induced by myogenic factors and ET-1. Clinical studies showed that intestinal blood flow increases with advancing post-natal age, possibly indicating maturation of vasodilator forces. Although no causal relation between intestinal blood flow and NO production has been demonstrated, Reber et al. (60, 61) found that the post-natal increase in intestinal blood flow is paralleled by increases in NO production in neonatal swine. Reber et al. (9) hypothesized that loss of NO production may compromise intestinal oxygen delivery and thus contribute to intestinal injury in neonates. This hypothesis is supported by findings of Nowicki et al. (89) who showed that NO-mediated vasodilation was disrupted in human intestine resected for NEC. The pathophysiology of NEC is complex

**TABLE 2 |** Postnatal maturation of intestinal oxygenation mechanisms.

Year	Author	Species	n	Ages	Newborn	Adolescent/adult	Comparison
<b>Intrinsic mechanisms</b>							
1988	Crissinger et al. (45)	Swine	20	1, 3 d, 2 wk, 1 mo	Venous pressure elevations led to reductions in blood flow and increases in (a-v)O <sub>2</sub> . Oxygen uptake increased in animals aged 1 day and remained unchanged in animals aged 3 days. Total vascular resistance decreased in response to venous pressure elevation in animals aged 1 day and increased in animals aged 3 days.	Venous pressure elevation led to decreased blood flow, increased (a-v)O <sub>2</sub> and decreased oxygen uptake. Total vascular resistance increased in response to venous pressure elevations.	Venous pressure elevation led to greater reductions in blood flow and oxygen uptake in all older animals compared to animals at day 1. Predominance of metabolic factors at day 1 and myogenic factors in older animals is suggested as evidenced by the total vascular resistance.
1988	Nowicki et al. (46)	Swine	18	3, 35 d	Blood flow decreased in response to reductions in perfusion pressure. Oxygen uptake increased in response to reductions in perfusion pressure. Pressure-flow autoregulation was absent.	Blood flow decreased in response to reductions in perfusion pressure. Oxygen uptake increased in response to reductions in perfusion pressure. Pressure-flow autoregulation was present.	Pressure-flow autoregulation was only present in older animals. Blood flow decreased and oxygen uptake increased to a similar extent in both age groups. As a consequence, oxygen uptake was more effectively maintained in older animals.
1990	Nowicki et al. (47)	Swine	26	3, 35 d	During free flow, blood flow decreased and (a-v)O <sub>2</sub> initially remained unchanged in response to venous pressure elevation, therefore oxygen uptake decreased. Greater venous pressure elevation led to increased (a-v)O <sub>2</sub> and maintained oxygen uptake.	During free flow, blood flow decreased and (a-v)O <sub>2</sub> remained unchanged in response to venous pressure elevation, therefore oxygen uptake decreased.	In response to venous pressure elevation, blood flow and oxygen uptake decreases to a greater extent in newborn animals.
1991	Nowicki et al. (48)	Swine	15	3, 35 d	Oxygen uptake decreased in response to arterial pressure reduction. Pressure-flow autoregulation was absent.	Oxygen uptake was maintained during arterial pressure reduction. Pressure-flow autoregulation was present and associated with venous PO <sub>2</sub> , but not with blood flow.	Pressure-flow autoregulation was only present in older animals. Oxygen uptake was only maintained in older animals.
1992	Nowicki et al. (49)	Swine	14	3, 35 d	Increased oxygen demand led to greater oxygen uptake resulting from increased (a-v)O <sub>2</sub> . Pressure-flow autoregulation was absent.	Increased oxygen demand led to greater oxygen uptake resulting from increased (a-v)O <sub>2</sub> . Pressure-flow autoregulation was present.	Pressure-flow autoregulation was only present in older animals.
1993	Nowicki et al. (50)	Swine	24	3, 35 d	Pressure-flow autoregulation was absent. The (a-v)O <sub>2</sub> increased in response to perfusion pressure reductions, but the magnitude of the increase diminished with lower pressures. Oxygen uptake decreased significantly in response to perfusion pressure reductions.	Pressure-flow autoregulation was present. The (a-v)O <sub>2</sub> increased in response to perfusion pressure reductions. Oxygen uptake only decreased in response to the greatest reduction in perfusion pressure	Pressure-flow autoregulation was only present in older animals. Oxygen uptake was only maintained in older animals.

(Continued)

TABLE 2 | Continued

Year	Author	Species	n	Ages	Newborn	Adolescent/adult	Comparison
1995	Nankervis et al. (51)	Swine	10	3, 35 d	Inhibited NO production increased vascular resistance and (a-v)O <sub>2</sub> , no changes in oxygen uptake were observed. Vasodilation was observed in response to increased flow. Inhibited NO production increased vascular resistance during increased flow rates.	Inhibited NO production did not affect vascular resistance, nor oxygen uptake. Vasodilation was observed in response to increased flow. Inhibited NO production did not have an effect on vascular resistance during increased flow.	Only in newborn animals, the NO-cGMP axis participates in setting basal vascular resistance and in flow-induced dilation. Flow-induced dilation was present in both age groups.
1997	Nakanishi et al. (52)	Rabbits	36	3–5 d, 4–8 mo	Inhibited Ca <sup>2+</sup> -influx caused vasorelaxation. Stimulated Ca <sup>2+</sup> -release from intracellular store sites caused vasoconstriction.	Inhibited Ca <sup>2+</sup> -influx caused vasorelaxation. Stimulated Ca <sup>2+</sup> -release from intracellular store sites caused vasoconstriction.	Newborn animals showed greater vasoconstriction in response to stimulated Ca <sup>2+</sup> -release from intracellular stores, whereas older animals showed greater vasorelaxation in response to inhibited Ca <sup>2+</sup> -influx through Ca <sup>2+</sup> -channels across the sarcolemma.
1998	Nowicki (53)	Swine	14	3, 35 d	Blood flow decreased, (a-v)O <sub>2</sub> increased and oxygen uptake decreased in response to reduced flow, achieved by perfusion pressure reductions. Vascular resistance increased in response to perfusion pressure reductions.	Blood flow decreased, (a-v)O <sub>2</sub> increased and oxygen uptake remained unchanged in response to reduced flow, achieved by perfusion pressure reductions. Vascular resistance increased in response to perfusion pressure reductions.	In newborn animals, vascular resistance increases to a greater extent in response to perfusion pressure reductions. Oxygen uptake is only maintained in older animals during perfusion pressure reductions.
1998	Reber et al. (54)	Swine	14	3, 35 d	Myogenic vasoconstriction in response to increased intravascular pressure was present. Flow-mediated dilation was present. Vasodilation was noted in response to combined increases in pressure and flow. Pressure-flow autoregulation was absent.	Myogenic vasoconstriction in response to increased intravascular pressure was absent. Flow-mediated dilation in response to increased flow was present. A modest degree of pressure-flow autoregulation was observed.	Myogenic vasoconstriction was only observed in newborn animals. A greater degree of flow-induced dilation was observed in newborn animals. Vasodilation in response to combined increases in pressure and flow was only observed in newborn animals. Pressure-flow autoregulation was only present in older animals.
1999	Nowicki (55)	Swine	50	3, 35 d	Vasoconstriction was observed in response to reduction of flow rate. Inhibited NO production increased vascular resistance. Low flow conditions caused increased vasoconstriction in response to ET-1 and these effect were even greater during inhibited NO production.	Vasoconstriction was observed in response to reduction of flow rate. Inhibited NO production increased vascular resistance. Low flow conditions did not alter the response to ET-1.	In newborn animals, low flow conditions caused greater vasoconstriction and a greater vasoconstrictor response to ET-1. Inhibited NO production increased vascular resistance to a greater extent in newborn animals.

(Continued)

TABLE 2 | Continued

Year	Author	Species	n	Ages	Newborn	Adolescent/adult	Comparison
2000	Nankervis et al. (56)	Swine	10	3, 35 d	Infusion of ET-1 caused vasoconstriction and decreased (a-v)O <sub>2</sub> . Oxygen uptake was compromised during ET-1 infusion. Blockade of ET <sub>A</sub> -receptors did not alter basal vascular tone. Blockade of ET <sub>B</sub> -receptors increased the extent of vasoconstriction, but had no effect on (a-v)O <sub>2</sub> .	Infusion of ET-1 caused vasoconstriction and decreased (a-v)O <sub>2</sub> . Oxygen uptake was compromised during ET-1 infusion. Blockade of ET <sub>A</sub> -receptors did not alter basal vascular tone. Blockade of ET <sub>B</sub> -receptors had no effect on vessel diameter, nor (a-v)O <sub>2</sub> .	In newborn animals, endogenous ET-1 participates in exchange vessel regulation, but not in setting basal vascular tone. Vasoconstriction caused by endogenous ET-1 is offset by vasodilation by activation of ET <sub>B</sub> -receptors, but only in newborn animals. In newborn animals, ET-1 infusion leads to greater increases in (a-v)O <sub>2</sub> .
2000	Nankervis et al. (57)	Swine	10	3, 35 d	Blockade of ET <sub>A</sub> -receptors did not alter basal vascular resistance, but increased oxygen uptake. Blockade of ET <sub>B</sub> -receptors and removal of the endothelium increased vasoconstriction in response to ET-1.	Blockade of ET <sub>A</sub> -receptors did not alter basal vascular resistance, nor oxygen uptake. Blockade of ET <sub>B</sub> -receptors and removal of the endothelium did not alter vasoconstriction in response to ET-1.	ET <sub>B</sub> -receptors are located on the endothelium and modulate the vasoconstrictor response to ET-1, but only in newborn intestine.
2001	Nankervis et al. (58)	Swine	10	1, 40 d	Myogenic vasoconstriction was observed in response to increased vascular pressure under no-flow circumstances, whereas vasodilation was observed in the presence of flow. Blockade of ET <sub>A</sub> -receptors caused vasodilation, but only in the absence of flow. Blockade of ET <sub>B</sub> -receptors and NO production caused vasoconstriction regardless of flow conditions.	Myogenic vasoconstriction in response to increased arterial pressure was absent, instead vasodilation was observed. Blockade of ET <sub>A</sub> -receptors, ET <sub>B</sub> -receptors and NO production produced no effect on vessel diameter.	Myogenic vasoconstriction in response to increased arterial pressure was only observed in newborn animals. In newborn animals, ET-1 participates in setting basal vascular tone, independent of the myogenic mechanism, that is offset by activation of ET <sub>B</sub> -receptors.
2001	Nankervis et al. (59)	Swine	12	1, 40 d	ET <sub>A</sub> -receptors were present and localized to vascular smooth muscle. ET <sub>B</sub> -receptors were present and localized to the endothelium.	ET <sub>A</sub> -receptors were present and localized to vascular smooth muscle. ET <sub>B</sub> -receptors were present and localized to the endothelium.	ET <sub>A</sub> - and ET <sub>B</sub> -receptors are present in a greater quantity in newborn intestine compared with mature intestine.
2001	Reber et al. (60)	Swine	10	3, 35 d	NO production increases and vascular resistance decreasing in response to increases in flow rate. Increased NO production was observed in response to decreases in flow rate, but vascular resistance remained unchanged.	NO production and vascular resistance remained unaltered in response to both increases and decreases in flow rate.	Basal NO production and stimulated NO production in response to increased flow rate were greater in newborn animals. Only in newborn animals, flow-induced dilation was observed.
2002	Reber et al. (61)	Swine	30	1, 3, 10, 30 d	Expression of eNOS protein was present. Blockade of NO production increased vascular resistance.	Expression of eNOS protein was present. Blockade of NO production increased vascular resistance at day 10, but not at day 30.	Expression of eNOS protein increased until day 10, but then decreased until day 30, whereas eNOS mRNA remained stable. Compared to 1-day-old animals, vascular resistance was higher in 30-day-old animals. Oxygen uptake increased until day 3, but then decreased until day 30.

(Continued)

TABLE 2 | Continued

Year	Author	Species	n	Ages	Newborn	Adolescent/adult	Comparison
2003	Su et al. (62)	Swine	40	1, 10 d	Vasoconstriction was observed in response to increased intravascular pressure. Blockade of PKC eliminated this vasoconstrictor response. Activation of PKC increased the contractile response.	No change in vessel diameter was observed in response to increased intravascular pressure. Neither blockade of PKC nor activation of PKC produced any changes in vessel diameter.	The intensity of myogenic vasoconstriction is greater in newborn animals. Myogenic vasoconstriction was attenuated by blockade and activation of PKC, but only in newborn animals.
2004	Su et al. (63)	Swine	12	3, 10, 30 d	ET <sub>A</sub> - and ET <sub>B</sub> -receptor mRNA and protein expression was present. The ET <sub>A</sub> -receptor was localized to vascular smooth muscle and the ET <sub>B</sub> -receptor was localized to the endothelial layer.	ET <sub>A</sub> - and ET <sub>B</sub> -receptor mRNA and protein expression was present. The ET <sub>A</sub> -receptor was localized to vascular smooth muscle and the ET <sub>B</sub> -receptor was localized to the endothelial layer.	ET <sub>A</sub> - and ET <sub>B</sub> -receptor mRNA and protein expression was greater in newborn animals. Localization of ET <sub>A</sub> - and ET <sub>B</sub> -receptors was similar.
2005	Wendel et al. (64)	Rats	15	0, 5, 14, 21, 28 d, adult	ET <sub>B</sub> -receptors were absent on smooth muscle cells in the mesenteric circulation	From day 14, ET <sub>B</sub> -receptors were present on smooth muscle cells of mesenteric arterioles, but not arteries and veins	ET <sub>B</sub> -receptors are only present on smooth muscles cells of mesenteric arterioles in mature intestine
2020	Ayuso et al. (65)	Swine	22	0, 3, 8, 19 d	In LBW animals, eNOS is present at birth in a moderate degree. In NBW animals, eNOS expression peaks at birth.	In both LBW and NBW, animals, eNOS expression is present in a moderate degree.	eNOS expression is greater in newborn animals than in mature animals, but only in NBW animals.
<b>Extrinsic mechanisms</b>							
1985	Buckley et al. (66)	Swine	34	1, 2–4 d, 1, 2 wk, 1 mo	An increase in vascular resistance was observed in response to inhibition of the baroreceptor reflex, achieved by occlusion of the carotid arteries. The circulation is under neural vasoconstrictor tone, as evidenced by decreased vascular resistance in response to section of the splanchnic nerve. SpNS produced vasoconstriction.	An increase in vascular resistance was observed in response to inhibition of the baroreceptor reflex, achieved by occlusion of the carotid arteries. The circulation is under neural vasoconstrictor tone, as evidenced by decreased vascular resistance in response to section of the splanchnic nerve. Increased vascular resistance was observed in response to SpNS and MNS.	The mesenteric circulation participated in the baroreceptor reflex in all age groups. Neural factors participate in setting basal vascular tone from birth onwards, but the decrease in vascular resistance observed in response to splanchnic nerve section was greater in older animals. Vascular resistance increased to a greater extent in older animals in response to SpNS.
1987	Buckley et al. (67)	Swine	34	6 h–2 d, 4–7 d, 2 wk, 1, 2 mo	Inhibition of the baroreceptor reflex increased vascular resistance. Severing the major components of the innervation increased flow. Vasoconstriction was observed in response to mesenteric nerve stimulation. Autoregulatory escape in response to sustained MNS was not observed.	Inhibition of the baroreceptor reflex increased vascular resistance. Severing the major components of the innervation increased flow. Vasoconstriction was observed in response to mesenteric nerve stimulation. Autoregulatory escape in response to sustained MNS was observed.	From birth, the mesenteric circulation is under neural vasoconstrictor tone and participates in the baroreceptor reflex. The increase in vascular resistance was greater and the latencies for the onset of vasoconstriction in response to MNS were smaller in older animals. From the age of 2 weeks, autoregulatory escape during sustained MNS is demonstrable and it is well-established by the end of the first month.

(Continued)

TABLE 2 | Continued

Year	Author	Species	n	Ages	Newborn	Adolescent/adult	Comparison
1991	Nowicki et al. (68)	Swine	22	3, 35 d	Vasoconstriction was observed in response to MNS. Autoregulatory escape was observed in response to sustained MNS, however oxygen uptake remained below baseline.	Vasoconstriction was observed in response to MNS. Autoregulatory escape was observed in response to sustained MNS, however oxygen uptake remained below baseline.	Sustained MNS produced similar effects on vascular resistance and oxygen uptake in newborn and older animals. Both age groups demonstrated autoregulatory escape.
1996	Hoang et al. (69)	Swine	22	0–2, 10–14 d	Neither $\alpha_1$ - and $\alpha_2$ -adrenoceptors seem to play a role in the vasoconstrictor response to $\alpha_1$ - and $\alpha_2$ -agonists, as evidenced by an unaltered response in the presence of $\alpha_1$ - and $\alpha_2$ -antagonists.	Specific, functional $\alpha_1$ - and $\alpha_2$ -adrenoceptors were present, as evidenced by blockade of the vasoconstrictor response to $\alpha_1$ - and $\alpha_2$ -agonists in the presence of $\alpha_1$ - and $\alpha_2$ -antagonists, respectively.	Selectivity of $\alpha_1$ - and $\alpha_2$ -adrenoceptor activity was only observed in older animals.
1998	Nowicki (70)	Swine	10	3, 35 d	SP is present. Infusion of SP causes vasodilation and increases oxygen uptake. Blockade of SP NK-1 receptors increases basal vascular resistance. Blockade of NO production eliminates SP-induced vasodilation and increases basal vascular resistance.	SP is present. Infusion of SP causes vasodilation and increases oxygen uptake. Blockade of SP NK-1 receptors did not alter basal vascular resistance. Blockade of NO production eliminates SP-induced vasodilation.	SP content is greater in newborn animals. SP participates in setting basal vascular resistance, but only in newborn animals.
2007	González-Luis et al. (71)	Swine	24	1, 2 wk	Electrical field stimulation, in the absence of cholinergic and adrenergic components, produced vasodilation, that was eliminated during blockade of NO production.	Electrical field stimulation, in the absence of cholinergic and adrenergic components, produced vasodilation.	Non-adrenergic, non-cholinergic relaxation was greater in newborn animals and was eliminated during blockade of NO production.

(a–v)O<sub>2</sub>: arteriovenous oxygen content difference, d, days, eNOS, endothelial isoform of NO synthase; ET, endothelin; LBW, low birth weight; MNS, mesenteric nerve stimulation; mo, month; NBW, normal birth weight; NO, nitric oxide; PKC, protein kinase C; PO<sub>2</sub>, partial pressure of oxygen; SP, Substance P; SpNS, splanchnic nerve stimulation; wk, week.

**TABLE 3** | Clinical studies in preterm neonates.

Year	Author	Population	n	Measurements	Postnatal changes
<b>Doppler</b>					
1990	Van Bel et al. (16)	Preterm and term (GA 24–43 wk)	91	1–5, daily	PI increased between 1 and 6 days. No significant changes were observed for PSV, TAMV, and EDV. Values for PSV, TAMV, and EDV increased with advancing GA. PI was not associated with GA. In SGA infants, EDV was significantly higher on day 1 and PI was significantly lower on days 1–2 compared to AGA infants.
1992	Coombs et al. (72)	Preterm (GA 27–35 wk) and term (GA 37–41 wk)	18	1, 2, 4 d	In term infants, an increase in PSV was observed between 1 and 2 days. In preterm infants, no significant changes were observed in PSV between 1 and 4 days. No significant difference was observed for PSV between term and preterm infants.
1996	Martinussen et al. (73)	Preterm (GA 33–35 wk)	15	1–7 d, daily	An increase in TAMV and EDV was observed between 1 and 2 days. EDV was positive in all infants examined between 6 and 24 h. No changes were observed after day 3.
1999	Maruyama et al. (74)	Preterm (GA 28–33 wk)	44	1–6 d, daily	An increase in TAMV was observed between 1 and 6 days. A decrease in RI was observed between 1 and 2 days, and then an increase to 6 days. A decrease in RVR was observed between 1 and 6 days.
1999	Yanowitz et al. (75)	VLBW (BW 750–1,250 g)	20	6, 30, 54 h, 7, and 14 d	An increase in TAMV was observed between 6 h and 7 days and between 6 h and 14 days. No significant changes were observed in EDV and RVR.
2001	Maruyama et al. (76)	VLBW, SGA (BW <1,500 g and below the 10th percentile)	10	1–7 d, daily	An increase in PSV was observed between 1 and 6–7 days. An increase in TAMV was observed between 1 and 5–6 days. An increase in EDV was observed between 1 and 3–7 days. A decrease in RI was observed between 1 and 2–7 days. A decrease in RVR was observed between 1–6 days. PSV, TAMV, and EDV were lower in SGA infants compared to AGA infants.
2006	Havranek et al. (77)	Preterm (GA <34 wk)	25	1–5 d, daily	An increase in PSV and TAMV was observed between 1 and 5 days.
2009	Papacci et al. (78)	Preterm (GA 25–28 wk, 29–32 wk, 33–36 wk) and term (GA 37–41 wk)	69	1, 3, 7, 14, 21, and 28 d	An increase in PSV, EDV and TAMV was observed between 1 and 28 days. Values for PSV, EDV, and TAMV increased with advancing GA. No changes in PI or RI were observed.
2012	Havranek et al. (79)	VLBW (BW <1,500 g)	35	1, 3, 5, 7, 10, and 14 d	An increase in PSV and TAMV was observed between 1 and 14 days. Lower values on day 1 were associated with higher post-natal increases in PSV and TAMV. No change in EDV was observed. No correlation was found between GA and day 1 PSV and TAMV.
2014	Thompson et al. (80)	Preterm (GA <27 wk, 27–31 wk, and 31–36 wk)	41	1, 1–4, 5–7, 8–14, and 15–28	No differences were observed in PSV on day 1 between GA groups. However, on day 5–7 and 8–14 higher GA was associated with higher PSV.
2015	Gursoy et al. (81)	Preterm (GA 26–34 wk)	25	1–5 d, daily	An increase in PSV, TAMV and EDV was observed between 1 and 5 days. A decrease in RI was observed between 1 and 5 days.
2018	Kocvarova et al. (82)	Preterm (GA 34–37 wk) and term (GA 38–42 wk)	40	2, 24, and 72 h	An increase in PSV was observed between 2 and 72 h. An increase in EDV was observed between 2 and 24 h. All EDV values were positive at 24 h. An increase in TAMV was observed between 2 and 24 h and between 24 and 72 h. A decrease in PI and RI was observed between 2 and 24 h. Preterm infants had lower PI at 2 h and higher PSV and EDV at 24 h compared to term infants.

(Continued)

TABLE 3 | Continued

Year	Author	Population	n	Measurements	Postnatal changes
<b>NIRS</b>					
2010	Cortez et al. (83)	Preterm (GA $\leq$ 30 wk)	19	48 h-14 d, continuously	A decrease in daily mean $r_sSO_2$ was observed between 48 h until 9 days, and then an increase between 10 and 14 days.
2011	McNeill et al. (84)	Preterm (GA 29–30 wk and 32–33 wk)	12	0–21 days, continuously	A decrease in daily mean $r_sSO_2$ was observed between 1 and 7 days in infants with GA 29–30 wk and between 1 and 4.5 days in infants with GA 32–33 wk. Afterwards, an increase in $r_sSO_2$ was observed. Lower GA was associated with lower $r_sSO_2$ values.
2014	Patel et al. (85)	Preterm (GA $<$ 32 wk and birth weight $<$ 1,500 g)	92	0–7 d, 5 min daily	An increase in mean $r_sSO_2$ was observed between 1 and 3 days. Afterwards, a decrease in $r_sSO_2$ was observed.
2016	Bozzetti et al. (86)	Preterm (GA 29–33 wk)	20	0–24, 48–72, 3 h daily	A decrease in $r_sSO_2$ was observed between 0–24 h and 48–72 h. In IUGR infants $r_sSO_2$ was significantly lower compared to non-IUGR infants.
2017	Ledo et al. (87)	Preterm (GA $<$ 32 wk)	72	36 h-7 d, continuously	An initial decrease in $r_sSO_2$ was observed for all infants, regardless of DA status. An increase in $r_sSO_2$ was observed after closure of the DA at day 3. No increase in $r_sSO_2$ until day 7 was observed in infants with persistent hsPDA.
2019	Kuik et al. (88)	Preterm (GA $<$ 30 wk, or birth weight $<$ 1,000 g, or GA $<$ 32 wk and birth weight $<$ 1,200 g)	29	2–5, 8, 15, 22, 29, 36 d, 2 h on each day	Generally, an increase in $r_sSO_2$ was observed between 2 and 36 days, with the lowest values on day 4 and day 15.

BW, birth weight; d, days; DA, ductus arteriosus; EDV, end-diastolic velocity; GA, gestational age; h, hours; NIRS, near-infrared spectroscopy; PI, pulsatility index; PSV, peak systolic velocity; RI, resistance index;  $r_sSO_2$ , splanchnic oxygen saturation; RVR, relative vascular resistance; TAMV, time-averaged mean velocity; VLBW, very low birth weight; wk, weeks.

and has not been fully elucidated, but may include impaired intestinal microcirculation (14). In preterm neonates, loss of NO production may thus predispose the intestine to hypoxic tissue injury, possibly contributing to the development of NEC.

We acknowledge some limitations. First, our review describes the mechanistic strategies available to neonatal and mature intestine to maintain adequate oxygenation, but does not include the contribution of these strategies during external influences that may alter intestinal oxygen supply or demand, e.g., anemia and enteral feeding. Nevertheless, our speculations on implications of these external influences on intestinal oxygenation are supported by recent reviews in both animal models and preterm neonates (18, 19, 44). Second, we purposely did not take into account factors that may influence the maturation processes described. These factors may include structural maturation and growth of intestinal tissue and vascularization networks, microbial colonization, and increasing volumes of enteral feeding (6, 90–92). Third, inherent limitations in Doppler and NIRS techniques complicate the translation to clinical implications. Doppler requires trained personnel, is prone to operator-dependent bias and provides only momentary blood flow velocity measurements of large vessels, whereas NIRS is challenged by intraindividual variability and interference of other tissues, intestinal contents and bowel movements with splanchnic oxygen saturation measurements (18). Finally, translation of our findings, derived from animal studies, to implications for preterm neonates is complicated by interspecies differences. By using NIRS to more regularly monitor  $r_sSO_2$  in preterm neonates, we may be able to learn more about the maturational phenomena described previously. For instance, it

may provide insight in the influence of GA and post-natal age on basal intestinal oxygenation and it may be used to study the response to external influences that alter oxygen supply or oxygen demand. At the same time, a better understanding of post-natal maturation of intestinal oxygenation mechanisms may facilitate interpretation of  $r_sSO_2$  and advance the use of NIRS in a clinical setting. Ultimately, bedside  $r_sSO_2$ -monitoring may lead to more streamlined and personalized care practices for at-risk neonates.

In conclusion, preterm intestine may have a smaller reserve for perturbations in intestinal oxygen delivery and oxygen demand, as oxygen extraction may be already be maximized under baseline circumstances. Developing additional understanding on this delicate balance of oxygen supply and demand may help in guiding clinical management to prevent intestinal tissue hypoxia.

## AUTHOR CONTRIBUTIONS

BD and EK conceptualized and designed the study. BD screened databases for eligible studies, drafted the initial manuscript, and revised the manuscript after feedback from coauthors. JMí, JMo, JH, AB, and EK critically reviewed the article. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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