Impact of Continuous vs Bolus Feeding on Splanchnic Perfusion in Very Low Birth Weight Infants: A Randomized Trial

Valentina Bozzetti, PhD[1], Giuseppe Paterlini, MD[1], Paola De Lorenzo, PhD[2,3], Diego Gazzolo, MD[4], Maria Grazia Valsecchi, PhD[3], and Paolo E. Tagliabue, MD[1]

Objective To detect changes in splanchnic perfusion and oxygenation induced by 2 different feeding regimens in infants with intrauterine growth restriction (IUGR) and those without IUGR.

Study design This was a randomized trial in 40 very low birth weight infants. When an enteral intake of 100 mL/kg/day was achieved, patients with IUGR and those without IUGR were randomized into 2 groups. Group A (n = 20) received a feed by bolus (in 10 minutes), then, after at least 3 hours, received the same amount of formula by continuous nutrition over 3 hours. Group B (n = 20) received a feed administered continuously over 3 hours, followed by a bolus administration (in 10 minutes) of the same amount of formula after at least 3 hours. On the day of randomization, intestinal and cerebral regional oximetry was measured via near-infrared spectroscopy and Doppler ultrasound (US) of the superior mesenteric artery was performed. Examinations were performed before the feed and at 30 minutes after the feed by bolus and before the feed, at 30 minutes after the start of the feed, and at 30 minutes after the end of the feed for the 3-hour continuous feed.

Results Superior mesenteric artery Doppler US showed significantly higher perfusion values after the bolus feeds than after the continuous feeds. Near-infrared spectroscopy values remained stable before and after feeds. Infants with IUGR and those without IUGR showed the same perfusion and oxygenation patterns.

Conclusion According to our Doppler US results, bolus feeding is more effective than continuous feeding in increasing splanchnic perfusion. *(J Pediatr 2016;176:86-92)*.

Trial registration ClinicalTrials.gov: NCT01341236.

There is little information regarding the impact of enteral feeding method on intestinal blood flow, and no consensus regarding whether bolus or continuous feeding is optimal. In many neonatal intensive care units (NICUs), feeds are administrated by bolus or continuous infusion without any standardized protocol.[1] There are theoretical benefits and risks with both kinds of feedings. Continuous enteral feeding might reduce feeding intolerance, improve nutrient absorption, and improve growth; however, it also could alter the cyclical pattern of release of gastrointestinal and pancreatic hormones and possibly interfere with growth. In contrast, feeding by bolus promotes the cyclical surges of hormones in healthy term infants; however, functional limitations of the premature infant's gastrointestinal system, such as delayed gastric emptying or intestinal transit, could hinder the preterm infant's ability to handle bolus milk feeds, resulting in feeding intolerance. In addition, this feeding regimen may challenge the preterm infant's ability to maintain metabolic homeostasis and achieve growth.[2-9]

Intrauterine growth restriction (IUGR) is a serious and common problem in obstetrics and in the NICU.[10] Placental dysfunction can impair fetal cardiovascular adaptation, characterized by a redistribution of cardiac output to maintain oxygen supply to the heart, adrenal glands, and brain at the expense of visceral organs (eg, the gastrointestinal tract). This condition, when associated with abnormal antenatal Doppler ultrasound (US)-measured flow velocity in the descending aorta or umbilical arteries, may predispose infants with IUGR to impaired gut function after birth.[11]

The superior mesenteric artery (SMA) is the major source of blood for the small intestine and large part of the colon. There is evidence indicating that the rate of increase in SMA blood flow velocity (BFV) as measured by Doppler US is correlated with a tolerance to enteral feedings.[12] Although numerous factors are known to affect intestinal blood flow,[13-22] little is known about

BFV	Blood flow velocity	PSV	Peak systolic velocity
CSOR	Cerebrosplanchnic oxygenation ratio	RI	Resistive index
EDV	End-diastolic velocity	$rSaO_2$	Regional abdominal oxygen saturation
FTOE	Fractional tissue oxygen extraction		
IUGR	Intrauterine growth restriction	$rScO_2$	Regional cerebral oxygen saturation
MV	Mean velocity	SMA	Superior mesenteric artery
NEC	Necrotizing enterocolitis	US	Ultrasound
NICU	Neonatal intensive care unit	VLBW	Very low birth weight
NIRS	Near-infrared spectroscopy		

From the [1]Neonatal Intensive Care Unit, MBBM Foundation, San Gerardo Hospital, Monza, Italy; [2]Department of Pediatrics, Centro Ricerca Tettamanti, University of Milano-Bicocca, San Gerardo Hospital; [3]Center of Biostatistics for Clinical Epidemiology, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; and [4]Department of Maternal, Fetal, and Neonatal Medicine, C. Arrigo Children's Hospital, Alessandria, Italy

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.05.031

the response of SMA BFV in preterm infants according to different feeding modalities. Near-infrared spectroscopy (NIRS) is a continuous, noninvasive, real-time technique that measures living tissues oxygenation.[23] NIRS may be useful in detecting changes in splanchnic oxygen delivery and predicting splanchnic ischemia by measuring the ratio of splanchnic saturation to cerebral saturation, the cerebrosplanchnic oxygenation ratio (CSOR).[24]

The purpose of this randomized, clinical trial was to detect the changes in splanchnic oxygenation and perfusion induced by 2 different feeding regimens (bolus and continuous) through SMA Doppler US and NIRS in very low birth weight (VLBW) infants with or without IUGR.

Methods

This single-center, randomized, cross-over study was performed in the NICU of San Gerardo Hospital, MBBM Foundation, Monza, Italy. The hospital's Ethics Committee approved the study protocol. Inclusion criteria were birth weight between 700 and 1500 g, gestational age >25 weeks and 6 days, and written informed consent from parents. Exclusion criteria were major congenital abnormalities (eg, severe heart or cerebral disease, chromosomopathies, severe renal malformations, any gastrointestinal diseases), participation in other trials, significant multiorgan failure before trial entry (eg, perinatal asphyxia with renal, cardiac, or cerebral impairment; disseminated intravascular coagulation), and preexisting cutaneous disease preventing placement of the probe.

Infants affected by IUGR were eligible. For this study, IUGR was defined as (1) absent-reverse diastolic flow velocity in the umbilical artery seen on at least 50% of waveforms on at least 1 occasion during pregnancy, or (2) cerebral redistribution.[25]

Infants were eligible for randomization after receiving at least 100 mL/kg/day of enteral nutrition, with adequate ventilation (not intubated, not on nasal continuous positive airway pressure, and with an fraction of inspired oxygen <50%) and no evidence or suspicion of necrotizing enterocolitis (NEC). A randomized AB/BA cross-over design was used. Infants with and without IUGR were assigned at random to receive nutrition with bolus administration in 10 minutes and then, after at least 3 hours, the same amount of feed with continuous administration for 3 hours (bolus + continuous arm) or to receive nutrition in the reverse order (continuous + bolus arm).

All patients underwent a baseline evaluation in the first 72 hours of life, including cerebral, cardiac, and abdominal US. According to our protocol, enteral nutrition was initiated after 72 hours of life as minimal enteral feeding (ie, <20 mL/kg/day), followed by increases of 20 mL/kg/day, as tolerated. Feeding tolerance was defined by internal protocol according to the quantity and type of gastric residual. All infants started parenteral nutrition on the first day of life. They were fed with human milk, if available, or with a preterm formula (75-80 kcal/100 mL). Human milk was fortified after an enteral intake of 100 mL/kg/day was achieved. Enteral nutrition was administered via nasogastric tube.

On the day of randomization, intestinal and cerebral regional oximetry were measured via NIRS (INVOS-5100C; Medtronic, Minneapolis, Minnesota). NIRS sensors were placed over the abdomen (splanchnic bed) and on the forehead (cerebral bed) to measure cerebral regional oxygen saturation ($rScO_2$) and infraumbilical regional abdominal oxygen saturation ($rSaO_2$). The CSOR ($rSaO_2/rScO_2$) was calculated as well. To investigate the balance between oxygen delivery and oxygen consumption, splanchnic fractional tissue oxygen extraction (FTOE) was computed as $(SaO_2 - rSO_2) \times 100/SaO_2$. Tissue oximetry was measured before and 30 minutes after the start of the bolus feeds and before, 30 minutes after the start of, and 30 minutes after the end of the continuous feeds. Pulse oximetry was used to record peripheral hemoglobin oxygen saturation during the NIRS tracing. NIRS tracings were used only in the absence of desaturation (<85% peripheral saturation). Capillary hemoglobin concentration was measured on the day of the evaluation.

The BFV of the SMA was evaluated as peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (MV), and resistive index (RI), calculated as (PSV−EDV)/PSV. To image the SMA, the US transducer was placed on the midabdomen above the umbilicus. The SMA was identified at its origin from the aorta and measurements were performed a few millimeters from its origin. Echo Doppler measurements were performed by 2 experienced operators on 5 contiguous homogeneous waves with a duplex pulsed color Doppler US machine (iU22; Philips, Eindhoven, The Netherlands) with a convex 3.5-MHz transducer.

Randomization was by random permuted blocks using Ranlist version 1.0 (https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware.aspx?Software_Id=29) at the trial data center. Recruitment was faster than expected, and 40 patients were randomized in 1 year, compared with the initial goal of 20 patients in 2 years (78% power to show a mean CSOR cross-over difference of at least 0.13 with an SD of 0.20; 2-sided test with $\alpha = 0.05$). The impact of each nutrition modality on splanchnic perfusion and oxygenation was defined as the difference between preprandial and postprandial CSOR and Doppler US measurements, respectively. The primary endpoint was the cross-over difference between preprandial and postprandial CSOR under bolus and under continuous feeding. Secondary analyses included the cross-over difference of regional saturations ($rScO_2$ and $rSaO_2$) and of FTOE and Doppler measurements.

We applied a generalized linear model to analyze the primary and secondary endpoints based on cross-over differences, after checking for normality assumption.[26] We also fit models including a term to account for period effect and to test for carryover effect to the data. We used the Fisher exact test to assess the associations between patient characteristics and intrauterine growth status. All tests were 2-sided. Analyses were performed using SAS 9.2 (SAS Institute,

Cary, North Carolina) at the trial data center at University of Milano-Bicocca.

Results

Forty-four VLBW infants were admitted to our unit between November 2011 and November 2012, of whom 42 were eligible and enrolled, including 11 with IUGR and 31 without IUGR. Forty of the 42 patients were randomized and all but 1 infant received the assigned arm (**Figure 1**; available at www.jpeds.com).

Patient characteristics are summarized in **Table I**. Enrolled infants had a median gestational age of 29 + 4 (26 + 2 to 36 + 0) weeks and median birth weight of 1225 (780-1495) g. Results of Doppler US and NIRS examinations are summarized in **Figures 2** and **3** and **Tables II** and **III** (available at www.jpeds.com). Both PSV and EDV increased from prebolus to bolus measurements, by 60% and 50%, respectively. As a result, from prebolus to bolus measurements, the RI remained stable: RI difference, expressed as mean (SD) was 0.01 (0.06) (P = .1825); the same occurred for measurements performed precontinuous and postcontinuous feeding: RI difference, mean (SD) was -.01 (0.07) (P = .4076). PSV and EDV increased after continuous feeding, by 9% and 16%, respectively, and RI was slightly decreased (-0.01 ± 0.07). Similar to EDV, MV increased more after bolus feeding than after continuous feeding (44% vs 11%).

The mean PSV cross-over difference was 54.03 (95% CI, 34.12-73.94; $P < .0001$), indicating a greater increase after bolus nutrition compared with after continuous nutrition. The mean PSV cross-over difference was 35.56 (95% CI, −3.86 to 74.96) for the IUGR group and 61.04 (95%, 37.02-85.05) for the non-IUGR group (P = .25). The mean EDV cross-over difference was 6.02 (95% CI, 0.89-11.14; P = .02), indicating a greater increase after bolus nutrition. The mean RI cross-over difference was similar between groups at 0.02 (95% CI, −0.01 to 0.05; P = .16). Results for the MV were similar to those for EDV, with an MV cross-over difference of 6.04 (95% CI, −0.09 to 12.16; P = .05). For all variables analyzed, no influence of period or carry-over effect was detected. As an unplanned subgroup analysis, we also studied the impact of the type of nutrition on PSV (**Table IV**; available at www.jpeds.com). The increase in Doppler PSV after bolus vs continuous nutrition was not related to the type of milk fed; the PSV mean cross-over difference (95% CI) was similar after human milk and after formula nutrition (P = .767).

CSOR measured by NIRS remained stable after continuous and bolus feedings compared with prefeeding values (mean CSOR difference of -0.074 ± 0.150 after continuous feed and -0.005 ± 0.145 after bolus feed). The mean CSOR cross-over difference was 0.069 ± 0.228, indicating no significant difference after bolus vs continuous nutrition (P = .06). Our results did not change after adjusting for period effect (P = .06) or carryover effect (P = .06) using a regression model (data not shown). Intrauterine growth did not affect CSOR (P = .16).

Splanchnic oximetry evaluated by abdominal and cerebral FTOE revealed no significant difference between bolus and continuous feeding (mean cross-over difference of -0.059 ± 0.177 [P = .05] for abdominal FTOE and -0.017 ± 0.069 [P = .14] for cerebral FTOE). IUGR had no impact on abdominal and cerebral FTOE cross-over

Table I. Perinatal and clinical features of the randomized cohort, overall and by IUGR status

Characteristics	Total (n = 40)	IUGR (n = 11)	Non-IUGR (n = 29)	*P* value*
Prenatal characteristics, n (%)				
Preeclampsia	8 (20)	3 (27)	5 (17)	.66
Premature rupture of membranes	10 (25)	0	10 (34)	.04
Chorionamniositis	3 (8)	0	3 (10)	.55
Antenatal steroid use	32 (80)	6 (55)	26 (90)	.02
Perinatal characteristics				
Cesarean delivery, n (%)	26 (65)	10 (91)	16 (55)	.06
Umbilical arterial pH, median (range)	7.30 (7.03-7.45)	7.29 (7.17-7.37)	7.30 (7.03-7.45)	.29
5-min Apgar score, median (range)	9 (5-10)	9 (7-10)	8 (5-10)	.08
Postnatal characteristics				
Gestational age, wk + d, median (range)	29 + 4 (26 + 2 to 36 + 0)	29 + 5 (28 + 2 to 36 + 0)	29 + 3 (26 + 2 to 32 + 1)	.02
Birth weight, g, median (range)	1225 (780-1495)	1085 (780-1495)	1240 (866-1495)	.51
Male sex, n (%)	16 (40)	4 (36)	12 (41)	.99
Normal cerebral US, n (%)†	37 (95)	9 (90)	28 (97)	.45
Normal abdominal US, n (%)‡	38 (95)	10 (91)	28 (100)	.28
Clinical conditions, n (%)				
Respiratory distress syndrome	27 (64)	8 (73)	19 (66)	.99
Patent ductus arteriosus	13 (33)	1 (9)	12 (41)	.07
Sepsis (by clinical diagnosis or positive blood culture)	13 (33)	4 (36)	9 (31)	.99
NEC, Bell stage ≥2	2 (5)	1 (10)	1 (3)	.45
Periventricular/intraventricular hemorrhage	5 (13)	3 (27)	2 (17)	.11
Bronchopulmonary dysplasia	1 (3)	0	1 (3)	.99
Age at randomized feeds, d, median (range)	14 (8-40)	16 (10-40)	13 (8-26)	.17
Human milk at randomized feeds	27 (68)	10 (91)	17 (59)	.07

*P value for comparison of IUGR vs non-IUGR.
†One infant with IUGR was excluded because an examination was not performed.
‡One infant without IUGR was excluded because an examination was not performed.

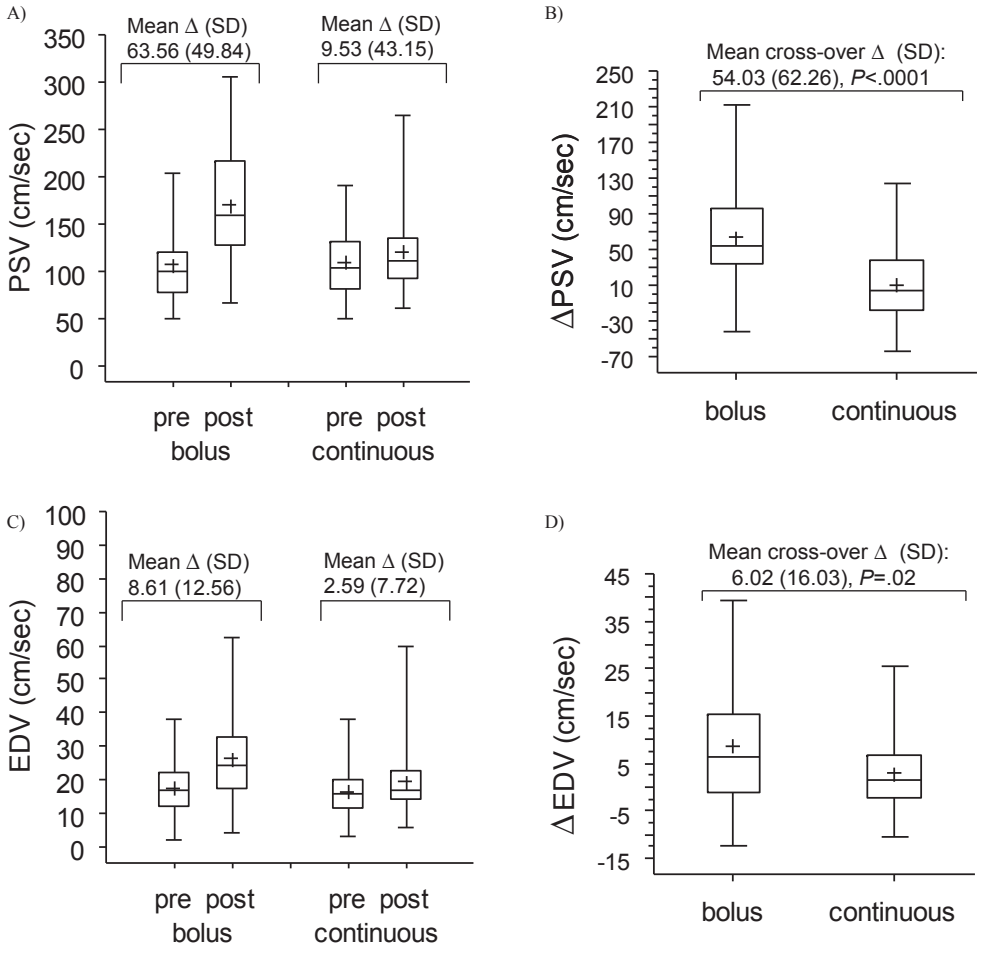

Figure 2. Doppler measurements taken prebolus and postbolus and precontinuous and postcontinuous feeding in 40 randomized patients, in terms of **A,** PSV, cm/s and **C,** EDV, cm/s, and the impact on Doppler measurements of bolus and continuous feeding in terms of differences in **B,** PSV, cm/s and **D,** EDV, cm/s. Δ is the difference between measurements taken after and before each feeding, and cross-over Δ is the difference of these differences.

differences (P = .20 and .72, respectively). Finally, we observed a modest effect of the type of milk. The CSOR mean cross-over difference was lower with human milk (0.006; 95% CI, −0.07 to 0.08) compared with formula milk (0.20; 95% CI, −0.05 to 0.35; P = .01) (**Table IV**).

Discussion

This study addresses important factors to consider in enteral nutrition for VLBW infants. Enteral feeding is one of the main factors involved in the onset of NEC,[27,28] owing in part to an imbalance between oxygen demand and supply. Oxygen supply is dependent on the route of feeding administration because it impacts splanchnic perfusion. Thus, the question of whether bolus feeding and continuous feeding have different effects on splanchnic oxygenation and perfusion has strong clinical relevance. A Cochrane Review comparing clinical effects of continuous and intermittent bolus nasogastric milk feeding in VLBW infants was inconclusive.[1]

In the present study, we compared the effect of bolus feeding and continuous feeding on postprandial perfusion and oxygenation using a randomized cross-over design, stratified by IUGR. Doppler US examination showed significantly increased BFV after bolus and continuous feedings, but the increases in all BFV measures were significantly higher after bolus feeding, consistent with previous studies.[29] The study of abdominal BFV in adults provides useful information about the mesenteric circulation in physiological and pathological situations.[30,31] Doppler US examination of the abdominal circulation in neonates has become a recognized technique for detecting impaired intestinal function.[32] Decreases in SMA BFV are associated with intestinal dysmotility,[33] feeding intolerance,[12,34,35] and risk of NEC.[32,36,37] Our findings in a cohort of VLBW infants revealed a hemodynamic response to a nutrient load in a physiological range.

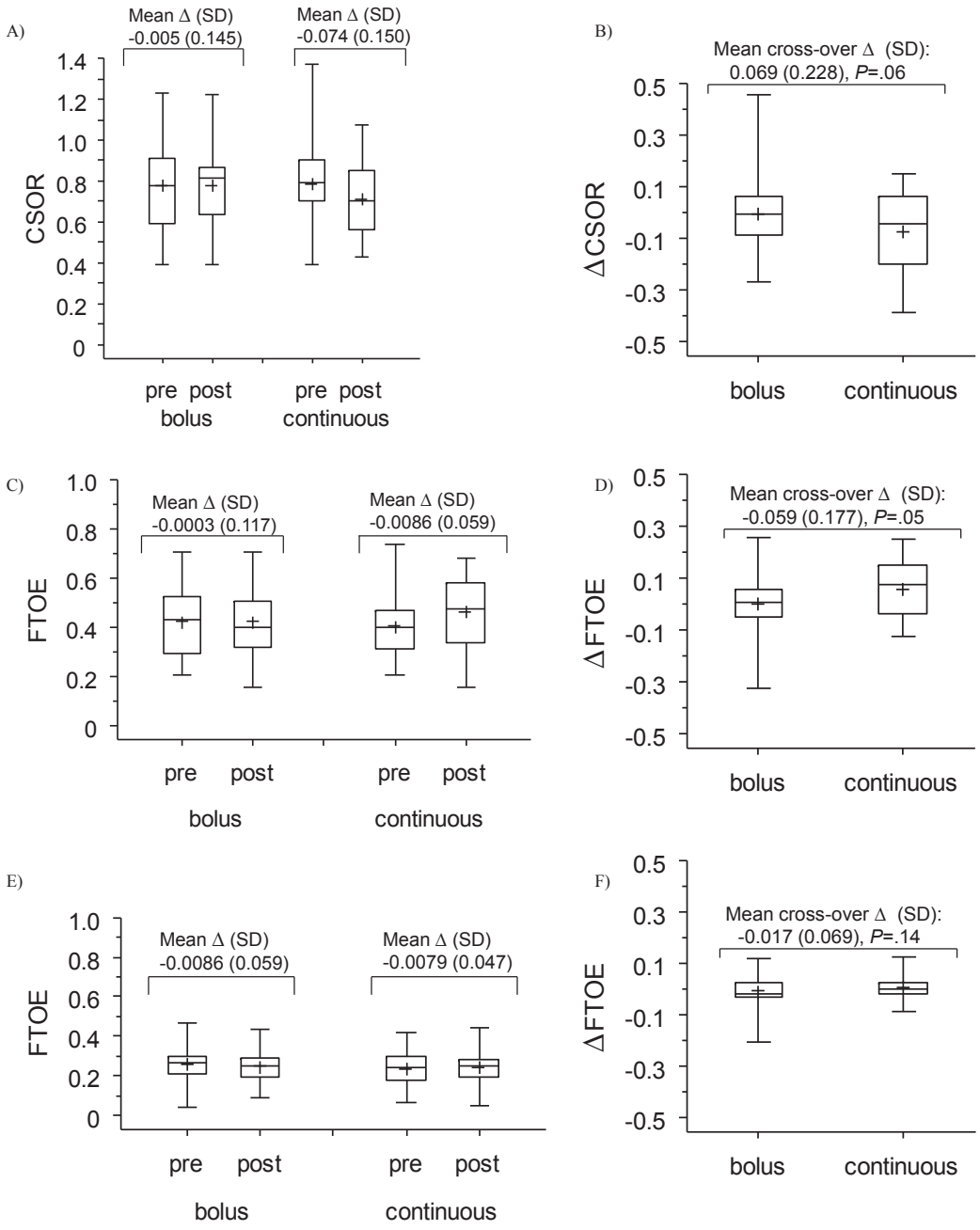

Figure 3. NIRS measurements taken prebolus and postbolus and precontinuous and postcontinuous feeding in 40 randomized patients, in terms of **A,** CSOR, **C,** splanchnic abdominal FTOE, and **E,** cerebral FTOE, and the impact on NIRS measurements of bolus and continuous feeding in terms of differences in **B,** CSOR, **D,** abdominal FTOE, and **F,** cerebral FTOE. Δ is the difference between measurements taken after and before each feeding, and cross-over Δ is the difference of these differences.

There are potential benefits to an increase in BFV, including increased nitric oxide activity, involved in intestinal functionality, and increased production of vascular endothelial growth factors.[38-40] Our findings suggest that feeding by bolus is more protective of the gastrointestinal tract, because a small or absent increase in mesenteric blood flow might not support the additional metabolic demand on the gut imposed by feeding.[41] The impaired splanchnic circulation in infants with IUGR with brain-sparing during the first days of life[11,42] might not be able to adequately increase blood supply in response to bolus feeding, however. Patients in our trial were evaluated while clinically stable, with no evidence of the diving effect or circulatory redistribution. We speculate that a greater increase in blood flow after bolus feeding likely results from the greater gastrointestinal workload during bolus feeding relative to continuous feeding.

In our trial, infants with IUGR and those without IUGR showed a similar pattern of BFV change after bolus and

continuous feedings, as was reported previously by Fang et al.[12] These data suggest that infants with IUGR are unable to develop the physiological postprandial increase of BFV in the SMA after the first feeding, but may acquire this ability later, when able to tolerate full orogastric feeds. In fact, in the trial, evaluations were done when infants were able to tolerate 100 mL/kg of enteral feeding, by which time the brain-sparing effect may have ceased.[42] Similar to previous studies,[12,29] we found no significant differences in postprandial MV, PSV, or EDV values between test feedings with breast or formula milk.

During bolus feedings, NIRS examination revealed stable CSOR values and abdominal saturation values after bolus feedings, and only minor decreases in CSOR and abdominal saturation values after continuous feedings. We used the CSOR for comparison because it is more reliable than splanchnic oxygenation value alone, and has been proposed as marker of abnormal perfusion processes affecting the gastrointestinal tract.[24]

Similar to previous studies,[43-45] in the present study brain tissue oxygenation remained stable following feedings. This stability is likely attributed to the physiological mechanism of cerebral self-regulation, which maintains cerebral blood flow and oxygen delivery at almost constant levels. Moreover, FTOE, which estimates the amount of oxygen extracted and describes the balance between local oxygen delivery and consumption, remained stable before and after feeding. Stable splanchnic oxygenation levels in the presence of increased SMA BFV would also support the view that the extra energy demand required by the gut for digestive and endocrine activity[44] was adequately met by the splanchnic blood flow, and that an additional increase in oxygen extraction by the intestine was not required. A mild increase in splanchinc oxygenation was observed after feeding with formula milk compared with breast milk. Keep in mind that the interpretation of NIRS data is difficult because of technical limitations.[46] As reported previously,[47] we obtained NIRS measurements at the lower NIRS sensitivity threshold ($rSaO_2$ at 15%), despite good sensor placement and absence of any pathological conditions, as well as periods with extreme variability.

Previously published studies in this area are scarce, not randomized, and present conflicting results. Dani et al[45] reported that bolus, but not continuous, milk feeding induced an increase in splanchnic oxygenation. Corvaglia et al[48] reported a significant decrease in splanchnic oxygenation occurring in the second half of continuous feeding and a slight trend toward increase in splanchnic tissue oxygenation index during the final 10 minutes of continuous feeding. Dave et al[46] reported increased CSOR by 1 hour after orogastric bolus feeding in stable preterm infants. In our trial, infants with IUGR and those without IUGR showed similar NIRS oxygenation patterns.

Because postnatal shunts through the patent ductus arteriosus may significantly decrease superior mesenteric blood flow during the first day of life, all infants enrolled in our study underwent echocardiography at randomization, which confirmed ductus closure in all infants.

Of note, bolus feeding was more effective than continuous feeding in increasing splanchnic flow. Bolus feeding may stimulate digestive and enzymatic activity of the gut and promote feeding tolerance; however, continuous feeding may be a more prudent approach in hemodynamically instable patients unable to respond to the feeding by increasing the blood flow in the SMA, such as preterm infants with perinatal ischemia, infants with IUGR with ongoing brain-sparing, and infants with gastrointestinal vascular dysfunction.

Limitations of this study include a lack of correlation between Doppler US and NIRS findings. Doppler examination is usually considered suboptimal because of high intraobserver variability, but this problem was limited in this study by having measurements performed by only 2 experienced clinicians. Instead, our experience with NIRS calls into question its reliability for monitoring gut oxygenation. Strengths of the study include its rigorous methodological and operative approach and our intensive investigation of multiple pathophysiologic variables.

In conclusion, we found that bolus and continuous feedings achieve a qualitatively similar effect on splanchnic blood flow, but with a more relevant effect after bolus feeding. Whether this effect translates to a clinical benefit for the patient is not known, because even more important than the absolute value of splanchnic blood flow is the relationship between oxygenation and the required intestinal endocrine and digestive work of the gut. Future research should focus on investigating the parallel hemodynamic and digestive/endocrine response to nutrient load and on identifying factors that predict the onset of the NEC. Our results suggest that bolus nutrition should be attempted in stable infants, with a switch to continuous nutrition in the event of cardiocirculatory impairment. ■

Submitted for publication Feb 1, 2016; last revision received Mar 30, 2016; accepted May 10, 2016.

Reprint requests: Valentina Bozzetti, PhD, Neonatal Intensive Care Unit, MBBM Foundation, San Gerardo Hospital, via Pergolesi 33, I-20900 Monza, Italy. E-mail: vbozzetti@hotmail.com

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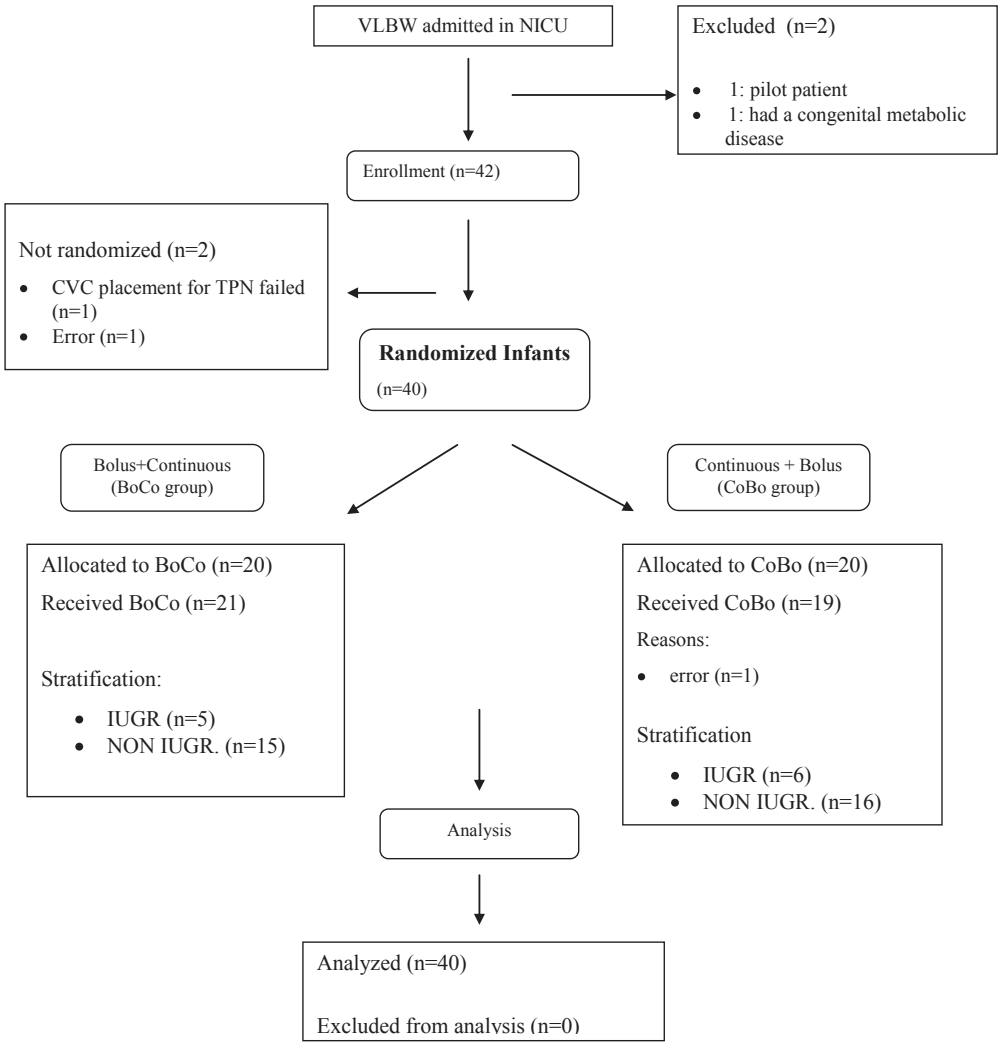

Figure 1. CONSORT diagram. *CVC*, central venous catheter; *TPN*, total parenteral nutrition.

Table II. Changes in BFV induced by bolus feeds and continuous feeds

Variables	PSV, cm/s	EDV, cm/s	RI	MV, cm/s
Prebolus	106.01 (35.14)	17.47 (7.52)	0.83 (0.07)	17.61 (9.38)
Postbolus	169.57 (55.17)	26.07 (13.50)	0.84 (0.07)	25.29 (13.73)
Difference, postbolus vs prebolus	63.56 (49.84)	8.61 (12.56)	0.01 (0.06)	7.67 (16.33)
Precontinuous	108.83 (34.07)	16.39 (7.25)	0.84 (0.06)	15.52 (7.76)
Postcontinuous	118.36 (43.50)	18.98 (9.41)	0.84 (0.06)	17.16 (9.99)
Difference, postcontinuous vs precontinuous	9.53 (43.15)	2.59 (7.72)	−0.01 (0.07)	1.64 (8.94)
Cross-over difference, bolus–continuous	54.03 (62.26)	6.02 (16.03)	0.02 (0.10)	6.04 (19.15)

Data are mean (SD).

Table III. Changes in abdominal rSO_2, cerebral rSO_2, and CSOR induced by bolus and continuous feeding in 40 randomized patients

	$rSaO_2$, %	$rScO_2$, %	CSOR
Prebolus	55.4 (13.6)	71.3 (8.1)	0.78 (0.20)
Postbolus	55.3 (12.9)	72.1 (8.9)	0.77 (0.19)
Difference, postbolus vs prebolus	−0.07 (10.98)	0.82 (5.6)	−0.01 (0.15)
Precontinuous	56.9 (12.2)	73.29 (8.2)	0.78 (0.18)
Postcontinuous	51.4 (12.8)	72.7 (8.0)	0.71 (0.16)
Difference, postcontinuous vs precontinuous	−5.48 (10.33)	−0.53 (4.53)	−0.07 (0.15)
Cross-over difference, bolus–continuous	5.41 (17.02)	1.35 (6.36)	0.07 (0.23)

Data are mean (SD).

Table IV. Effects of type of nutrition (human vs formula milk) on PSV Doppler and CSOR

	Human (n = 13)	Formula (n = 27)	*P* value
PSV	56.09 (30.13 to 82.05)	49.74 (15.35 to 84.12)	.767
CSOR	0.006 (−0.07 to 0.08)	0.20 (−0.05 to 0.35)	.01

Data are mean cross-over difference (95% CI).