

# Prediction of early tolerance to enteral feeding in preterm infants by measurement of superior mesenteric artery blood flow velocity

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## Abstract

**Aims**—To evaluate whether serial Doppler measurements of superior mesenteric artery (SMA) blood flow velocity after the first enteral feed could predict early tolerance to enteral feeding in preterm infants.

**Methods**—When clinicians decided to start enteral feeds, Doppler ultrasound blood flow velocity in the SMA was determined before and after a test feed of 0.5 ml milk. The number of days taken for infants to tolerate full enteral feeding (150 ml/kg/day) was recorded.

**Results**—Fourteen infants (group 1) achieved full enteral feeding within seven days. Thirty infants (group 2) took 8–30 days. There was no difference in the preprandial time averaged mean velocity (TAMV) between the groups at a median age of 3 (2–30) days. In group 1, there was a significant increase in TAMV ( $p < 0.01$ ) above the preprandial level at 45 and 60 minutes, but this did not occur in group 2. An increase in TAMV by more than 17% at 60 minutes has a sensitivity of 100% and a specificity of 70% for the prediction of early tolerance to enteral feeds.

**Conclusions**—There is a significant correlation between an increase in mean SMA blood flow velocity and early tolerance of enteral feeding. Doppler measurements of SMA blood flow velocity may be useful for deciding when to feed high risk preterm infants.

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Intestinal blood flow is regulated by intrinsic and extrinsic mechanisms as well as circulating vasoactive substances. Changes in superior mesenteric artery (SMA) blood flow velocity have been shown to occur in response to feeds.<sup>1-5</sup> Feed composition has been shown to affect this response but the precise mechanisms controlling the postprandial increase are poorly defined.

Blood flow disturbances, reperfusion injury, infection, and early enteral feeding have been hypothesised to be associated with necrotising enterocolitis.<sup>7</sup> In severely growth restricted infants, absent end diastolic flow in the fetal descending aorta and umbilical artery in antenatal Doppler studies has been shown to be associated with perinatal death, necrotising enterocolitis, and haemorrhage.<sup>8,9</sup> Although such findings may indicate that caution should be exercised when introducing early enteral

feeding, such feeding is important for the functional maturation of the gut in preterm infants.<sup>10</sup> For these reasons, the question of whether or not to feed a sick preterm infant remains a dilemma.

The aims of the study were to correlate changes in SMA blood flow velocity in response to a test feed with tolerance to enteral feeds and to establish whether serial Doppler measurements of SMA blood flow velocity could predict early tolerance to enteral feeding in preterm infants.

## Methods

This was a prospective blinded study, carried out at King's College Hospital, of 56 preterm infants all of whom were less than 36 weeks gestation. All infants were studied before they developed clinical abdominal signs or symptoms. The period of the study was from the time of a test feed to the time taken to achieve full enteral feeds of 150 ml/kg/day. The study was approved by the King's College Hospital ethics committee.

## TEST FEED AND DOPPLER MEASUREMENTS

When clinicians decided to start preterm infants on enteral feeds, parental consent was obtained to carry out a test feed. If previously inserted, umbilical artery catheters were removed at least 12 hours before the test feed. The test feed consisted of 0.5 ml breast or formula milk administered through the nasogastric tube. Breast milk was given when available. No infant had been enterally fed before the test feed. A preprandial measurement was taken, the milk was given, and postprandial measurements of SMA blood flow velocity were recorded at 15 minute intervals for 60 minutes.

Doppler measurements of the SMA blood flow velocity were recorded with a Hewlett-Packard Sonos 100 ultrasound machine with 5 MHz transducer and pass wall filter of 100 Hz. The SMA was visualised in the sagittal view just below the xiphisternum, and Doppler signals were sampled just distal to the origin of the SMA from the aorta using a sample of gate size 3 mm. The recordings were videotaped and analysed. The peak systolic velocity and end diastolic velocity were measured. The mean of five consecutive values of the peak systolic and diastolic velocity was calculated for analysis. The time averaged mean velocity (TAMV) was measured from the envelope of at least five cardiac cycles. Pourcelot's resistance index was calculated from the formula: (peak systolic velocity–end diastolic velocity)/peak systolic velocity. This measurement is related

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to the vascular resistance distal to the point of Doppler sampling.

Blood pressure, heart rate, packed cell volume, and temperature were recorded before the study. PaCO<sub>2</sub> was recorded in 28 infants from peripheral arterial lines.

#### FEED TOLERANCE AND OUTCOME

The clinicians were not aware of the results of the study. The milk was gradually increased by 0.5 ml every 4–12 hours if tolerated by the infants. Any abnormal abdominal signs and the number of days to achieve full enteral feeding were recorded.

The infants could be divided into two groups: group 1, early tolerance group—infants who tolerated full enteral feeds within seven days of starting the feeds; group 2, late tolerance group—infants who took longer than seven days to achieve full enteral feeds.

#### REPRODUCIBILITY OF THE MEASUREMENTS

All measurements were made by a single observer (SF) to eliminate interobserver variability. Serial measurements were taken to evaluate intersubject variability. Reproducibility of the measurement of SMA blood flow velocity was assessed by carrying out two preprandial measurements 10 minutes apart, with the probe removed and reapplied to the abdomen between readings. In total, 88 measurements were taken. The standard deviation of the difference between the mean for systolic velocity, end diastolic velocity, TAMV, and Pourcelot's resistance index were 8.2, 13.8, 8.7, and 4.1 respectively. From the reproducibility data, we calculated that a 17% change in the TAMV would be significant at a 95% confidence limit.

Results were analysed using Mann-Whitney, Fisher Exact, one way analysis of variation, linear regression, and correlation.

### Results

A total of 56 infants were enrolled in the study. Four died and eight did not have complete data or measurements. The 44 infants who completed the study (table 1) had a median (range) gestational age of 30 (25–36) weeks and birth weight 1155 (602–1542) g. The test feed was given at a median postnatal age of 3 (2–30) days. Thirty four infants had expressed breast milk, and 10 had formula milk for the test feeds. Of the 34 infants given expressed breast milk, 24 continued to be fed on expressed breast milk, and 10 on mixed breast and formula milk. The 10 infants test fed with formula milk continued to be given this milk. Twenty five infants were small for gestational

Table 1 Patient details at trial entry

	Whole group (n=44)	Group 1 (n=14)	Group 2 (n=30)
Gestational age (weeks)	30 (26–36)	30 (28–36)	30.5 (26–36)
Birth weight (g)	1155 (626–1542)	1144 (626–1542)	1174 (714–1524)
Postnatal age (days)	3 (2–30)	3 (2–25)	3 (2–30)
PDA	4	0	4
EBM	24	6	18
Formula	10	4	6
Mixed feeds	10	4	6

Where applicable, values are medians (interquartile range).

age (SGA) defined as birth weight below the 3rd centile. Four infants had patent ductus arteriosus.

Fourteen infants (group 1) took a median of 5 (4–7) days to achieve full enteral feeding (150 ml/kg/day). Thirty infants (group 2) took a median of 15 (9–30) days to achieve full enteral feeding. All the infants in group 2 had clinical signs and symptoms that resulted in feeds being stopped and restarted. Twenty eight had one or more of the following: abdominal distension, increasing volume of gastric aspirate or bile stained aspirate, and/or apnoea and bradycardia. Thirteen infants needed to be investigated for possible sepsis at a median of 5 (2–9) days after the test feed. These infants were in group 2.

#### REGRESSION ANALYSIS

##### Correlation between tolerance to enteral feeds and resistance index

Early tolerance to enteral feeds correlated significantly ( $r = 0.6$ ,  $p < 0.0001$ ) with a lower index of vascular resistance at 60 minutes after the test feed (fig 1).

##### Percentage change in TAMV from preprandial value

There was significant negative correlation ( $r = -0.49$ ,  $p < 0.001$ ) between the increase in TAMV at 60 minutes and the number of days taken to tolerate enteral feeds (fig 2). From the graph, all of the infants with lower TAMV at 60 minutes from the preprandial value took longer than seven days to achieve full enteral feeding.

There was no significant correlation between the days to achieve full feeding and the peak systolic velocity at 60 minutes after a test feed.

There was no significant correlation between the type of milk, birthweight centile, or whether the infants had a positive blood culture and tolerance to enteral feeds.

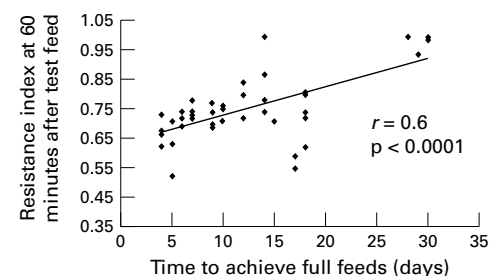


Figure 1 Pourcelot's resistance index at 60 minutes after a test feed and tolerance to enteral feeding.

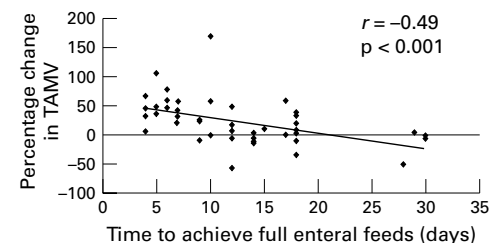


Figure 2 Percentage change in timed average mean velocity (TAMV) and tolerance to enteral feeds.

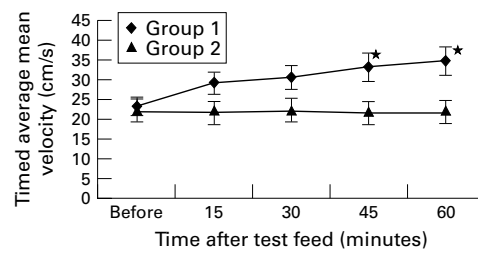


Figure 3 Mean (SD) timed average mean velocity in groups 1 and 2 before and at 15 minute intervals after the test feed. \* $p < 0.01$  compared with preprandial value.

#### DIFFERENCES BETWEEN EARLY (GROUP 1) AND LATE TOLERANCE (GROUP 2)

There was no difference between the groups with regard to gestational age, birth weight, postnatal age, postconceptual age, or Apgar scores.

There was no significant difference in the preprandial values of TAMV, peak and end diastolic velocity, and resistance index between groups 1 and 2. The infants in group 1 had a significant increase ( $p < 0.01$ ) in TAMV from the preprandial value after the test feed but there was no significant change in group 2 (fig 3). The TAMV at 45 and 60 minutes in group 1 was significantly higher than in group 2 ( $p < 0.01$ ).

There was no significant difference in the peak velocity or the resistance index between groups 1 and 2 at 60 minutes.

#### Breast or formula milk as test feed

There was no significant difference in the postprandial values of mean velocity, resistance index, or systolic or end diastolic velocity whether breast or formula milk were used for test feed.

#### SGA infants

There was no significant difference in the TAMV, peak velocity, or resistance index before or after a test feed in the SGA or appropriate size for gestational age (AGA) infants. There was no significant difference in the values for SGA defined as  $< 3^{\text{rd}}$  or  $< 10^{\text{th}}$  centile. There was no significant difference in the number of days taken to achieve full enteral feeding between the SGA and AGA infants.

#### PREDICTIVE VALUE OF POSITIVE HAEMODYNAMIC RESPONSE TO TEST FEED

From the reproducibility data, it was calculated that 95% of repeated measures of TAMV should be no more than 17% above the preprandial values. Changes greater than 17% represent a positive haemodynamic response to feeding.

Infants were divided into those showing a positive or absent haemodynamic response to feeding at each time point, and the numbers within each response group who tolerated their feeds in less than seven days were calculated (table 2). The response at 60 minutes was the most predictive of early feed tolerance, with a sensitivity of 100% and specificity of 70%. Infants who failed to show a positive haemodynamic response at 60 minutes all had delayed feed tolerance.

Table 2 Prediction of early tolerance to enteral feeds by measurement of blood flow velocity in superior mesenteric artery in response to test feed

Tolerance to enteral feeds	>17%	<17%	Total
<7 days after test feed	14	0	14
>7 days after test feed	9	21	30
Total	23	21	44

A positive haemodynamic response is considered to be a change in time averaged mean velocity of greater than 17%. Sensitivity, 100%; specificity, 70%; positive predictive value, 61%; negative predictive value, 100%.

#### Discussion

This study has shown that there is a significant correlation between early tolerance to enteral feeds and increase in SMA blood flow velocity at 60 minutes after the first test feed. The haemodynamic response to feeding is predictive of feed tolerance in this cohort of preterm infants. The lower resistance indices in babies with early tolerance of enteral feeds suggest that the haemodynamic response could be due to intestinal vasodilatation in this group of infants.

Despite its limitations in measuring velocity rather than volume flow, serial changes in SMA blood flow velocity could be shown in infants when feeds were first introduced. Enteral feeding stimulates intestinal motility and release of circulating vasoactive substances such as CCK-PZ, secretin, and gastrin.<sup>11-13</sup> Responses of intestinal peptides and motor activity depend on the type of enteral feed.<sup>10</sup> It is likely that, with milk feeds, the increase in peptide plasma concentrations and motor activity occur with an accompanying fall in vascular resistance and increased intestinal blood flow at 60 minutes after the test feed.

It was notable that infants who showed poor vasomotor response to feeding later more often showed clinical symptoms and signs of feed intolerance such as abdominal distension, increasing nasogastric aspirates, apnoea, and bradycardia. Almost half of these babies subsequently developed sepsis. Pathological changes in hypoxia, ischaemia, and underperfusion of the intestine may result in alteration in the interaction between intestinal motility and the release of vasoactive substances with enteral feeding. It is possible that the physiological changes in these unwell infants affect the motility and release of vasoactive substances, or the effect of the release of cytokines and inflammatory mediators may influence the response of SMA blood flow velocity to the first test feed.

Leidig<sup>3</sup> studied SMA blood flow velocity in preterm infants exposed to enteral feeds. Previous studies have shown that the type of enteral feed can affect intestinal blood flow.<sup>6,7</sup> Fasting velocities were 20% lower in breast fed than formula fed infants.<sup>7</sup> In our study, there was no difference in TAMV, peak systolic velocity, and Pourcelot's resistance index for those given breast or infant formula as test feed.

Coombs *et al*<sup>4</sup> showed the effects of patent ductus arteriosus and indomethacin on gut blood flow velocity. In our study, there were four infants with patent ductus arteriosus, who were treated with indomethacin at a median duration of four days before the first feed was

given. When the infants with patent ductus arteriosus were excluded, there was still a correlation between tolerance to enteral feeds and SMA blood flow velocity.

This study did not set out to compare the response of SGA or AGA infants to enteral feeds. The birth weights of the infants were not corrected for parental height or ethnicity. Previous studies<sup>15</sup> have shown that the mean velocity was lower in SGA infants, reflecting the reduction in visceral perfusion and fetal hypoxia. In this study, there were an equal number of SGA infants in groups 1 and 2. There was no difference in the response to enteral feeds between SGA and AGA infants. We do not have data on parental growth parameters or antenatal Doppler studies to determine whether this group of SGA infants was constitutionally small or growth restricted.

This is the first prospective study that examines the relation of serial Doppler measurements of SMA blood flow velocity to clinical abdominal symptoms and signs of intolerance to enteral feeds. The haemodynamic response to the first enteral feed could be used to assist the clinician to decide whether high risk infants could tolerate enteral feeds. In those with a poor response, the difficult question still needs to be faced as to whether total parenteral nutrition or minimal enteral feeding are the best treatments to allow the gut to mature to a point where enteral feeding can be safely tolerated.

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