INTRODUCTION

Caffeine and theophylline stimulate the respiratory center in the medulla of brain. This is associated with a regular breathing pattern, increased alveolar ventilation and decreased episodes of apnea. Caffeine has several advantages over theophylline such as a more reliable enteral absorption and longer half-life, thus requiring a less frequent dosing schedule with fewer side effects ***(Steer et al., 2000).*** Hence, caffeine is preferred over theophylline for treatment of apnea in preterm infants.

Erenberg et al. ***(Erenberg et al., 2000)*** have shown that a loading dose of 10 mg/kg of caffeine base followed by 2.5 mg/kg/day is safe and effective for treating apnea of prematurity. A single high loading dose of caffeine base 25 mg/kg has been reported to reduce the cerebral and intestinal blood flow velocities (BFV***) (Lane et al., 1999); (Hoecker et al., 2002)***. A divided high loading dose of 25mg/kg caffeine base given four hours apart was shown to decrease BFV in cerebral arteries after the second dose, whereas BFV in intestinal arteries was not affected ***(Hoecker et al., 2006).***

Uncontrolled, retrospective studies have shown that oral theophylline increases the risk of necrotising enterocolitis whereas intravenous theophylline did not ***(Robinson et al., 1980; Jones et al., 1981).***

A recent multicenter study showed that there is no increase in the incidence of necrotising enterocolitis with caffeine use ***(Schmidt et al., 2006).*** The impact of caffeine on superior mesenteric artery (SMA) BFV would help understand the degree to which blood flow in mesenteric arteries is altered, and if so the time taken for recovery to occur.

AIM OF THE WORK

This study aimed at investigating the effects of caffeine base given at a loading dose of 10 mg/kg(caffeine base) followed by maintenance dose of 2.5 mg/kg on SMA BFV in preterm infants.

SPLANCHNIC CIRCULATION IN THE NEONATE

I. Embryologic development of the celiac trunk and the superior mesenteric artery:

The primitive dorsal aorta gives rise to the abdominal aorta during fetal development. Ventral segmental arteries emerge from the primitive ventral aorta, which disappears around the fourth week of gestation. Multiple segmental branches from the primitive ventral aorta—the 10th, 13th, and 21st—persist and develop into the celiac artery, SMA, and inferior mesenteric artery (IMA), respectively. Disparity in the regression of the primitive ventral aorta and its segmental branches infrequently causes deviations in the visceral arterial anatomy. ***(Cronenwett & Johnston., 2014)***

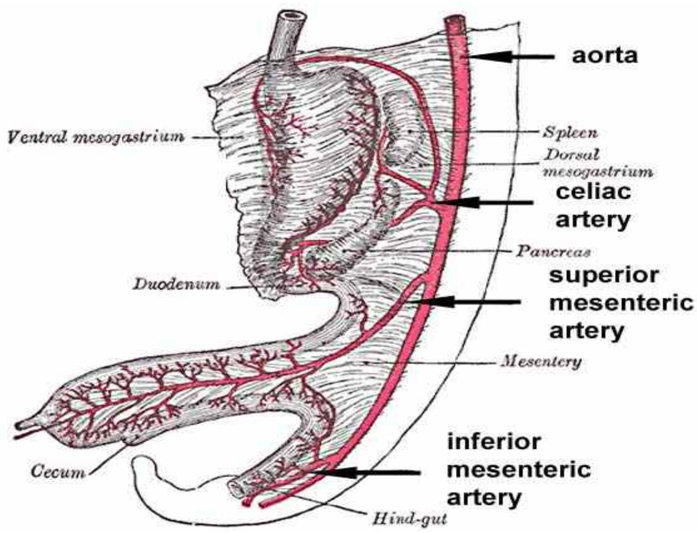

Figure (1): Blood supply to the gut ***(Gabella, 1995).***

II. Anatomy of the blood supply of the gut

Gastrointestinal blood flow the "Splanchnic circulation":

The blood vessels of the gastrointestinal system are part of a more extensive system called the splanchnic circulation; it includes the blood flow through the gut itself plus blood flow through the spleen, pancreas, and liver. The design of this system is such that all the blood that courses through the gut, spleen, and pancreas then flows immediately into the liver by way of the portal vein. In the liver, the blood passes through millions of minute liver sinusoids and finally leaves the liver by way of the hepatic veins that empty into the vena cava of the general circulation ***(Guyton and Hall, 2000)***.

Celiac trunk:

The celiac trunk is the first anterior branch of abdominal aorta and arises just below the aortic hiatus at the level of T12/L1 vertebral bodies It is 1.5–2 cm long and passes almost horizontally forwards and slightly right above the pancreas and splenic vein. It divides into:

- Left gastric.
- Common hepatic.
- Splenic arteries.

The superior mesenteric artery may arise with the coeliac trunk as a common origin ***(Stadring et al., 2008)***

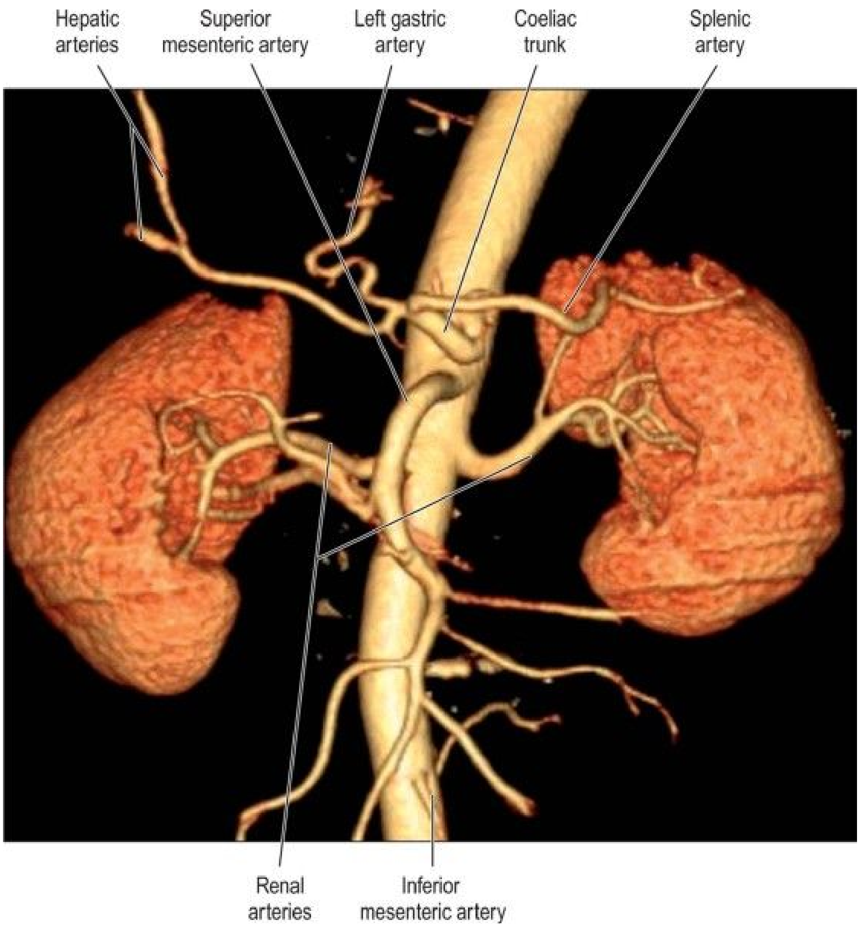

Figure (2): Volume rendered surface shaded CT angiogram of the major branches of the abdominal aorta (renal, coeliac and superior mesenteric arteries). (Courtesy of Dr Nasir Khan, Chelsea & Westminster Hospital, London.) ***(Stadring et al., 2008)***

Superior mesenteric artery:

The superior mesenteric artery is by far the most important of the arteries to the alimentary tract, as it supplies the whole of the small intestine from the superior part of the duodenum to the midtransverse colon, and is functionally an end artery. The superior mesenteric artery originates from the aorta 1 cm below the coeliac trunk. The angle of its origin from the aorta is acute. The artery runs inferiorly and anteriorly

. Its calibre progressively decreases as successive branches are given off to loops of jejunum and ileum, and its terminal branch anastomoses with the ileocolic artery.

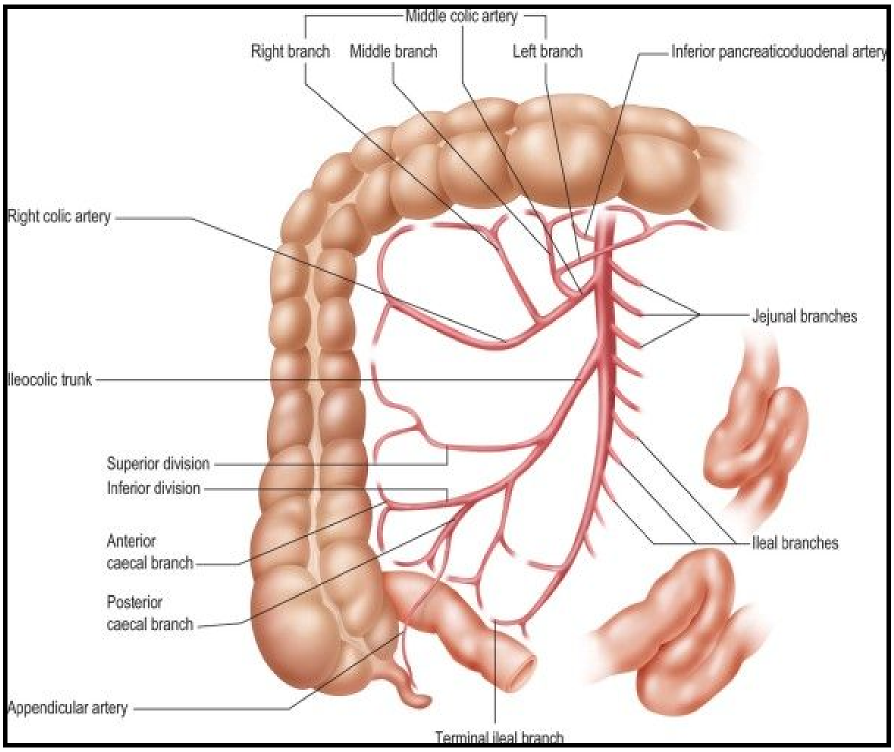

Figure (3): The superior mesenteric artery and its branches ***(Stadring et al., 2008)***

Branches of the superior mesenteric artery:

The superior mesenteric artery gives off:

- Middle colic.
- Right colic (sometimes).

- Ileocolic.
- Jejunal and ileal branches.

(Stadring et al., 2008)

Jejunal branches:

- There are usually five to ten jejunal branches which arise from the left side of the upper portion of the superior mesenteric artery (Fig). They are distributed to the jejunum as a series of short arcades which form a single (occasionally double) tier of anastomotic arcs before giving rise to multiple vasa recta (Fig. 66.8). These vessels run almost parallel in the mesentery and are distributed alternately to opposite aspects of its wall where the two series of vessels form distinct 'leaves' within the mesentery. Small twigs supply regional lymph nodes and other structures in the mesentery ***(Stadring et al., 2008)***

Ileal branches:

- Ileal branches are more numerous than the jejunal branches but smaller in calibre. They arise from the left and anterior aspects of the superior mesenteric artery. The length of the mesentery is greater in the ileum and the branches form three, four or sometimes five tiers of arcs within the mesentery before giving rise to multiple vasa recta that run directly towards the ileal wall. The ileal branches run parallel in the mesentery and are distributed to alternate aspects of the ileum .They are longer and smaller than similar jejunal vessels, particularly in the distal ileum, and do not form such definite parallel ‘leaves' of vessels ***(Stadring et al., 2008)***

Variations:

- It may be the source of the common hepatic, gastroduodenal, accessory right hepatic, accessory pancreatic or splenic arteries.

Superior mesenteric artery may arise from a common coeliacomesenteric trunk ***(Suzan et al., 2008).***

Inferior mesenteric artery:

- The inferior mesenteric artery supplies the left third of the transverse colon (figure), all the descending colon, sigmoid colon and most of the rectum ***(Gabella, 1995)***. The inferior mesenteric artery is usually smaller in calibre than the superior mesenteric artery. It arises from the anterior or left anterolateral aspect of the aorta at about the level of the third lumbar vertebra, 3 or 4 cm above the aortic bifurcation and posterior to the horizontal part of the duodenum ***(Stadring et al., 2008).***

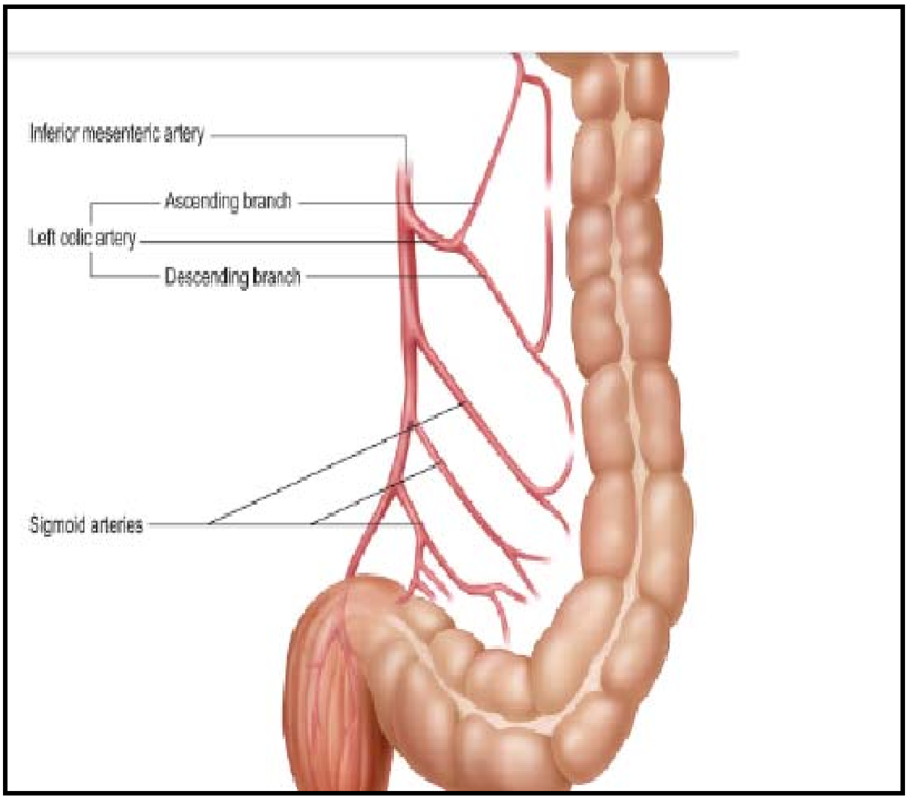

Figure (4): The inferior mesenteric artery ***(Stadring et al., 2008)***

III. <u>Anatomy and growth of neonatal intestine:</u>

Small intestine:

This forms an oval-shaped mass with a greater diameter transversely oriented in the abdomen rather than vertically as in the adult. The mass of the small intestine inferior to the umbilicus is compressed by the urinary bladder which is anterior at this point. The small intestine is 300-350 cm long at birth and its width when empty is 1-1.5 cm. The ratio between the length of the small and large intestine at birth is similar to the adult. The mucosa and the submucosa are fairly well developed with the villi throughout the small intestine (villi are present in the large intestine earlier in the development); however, the muscularis is very thin, particularly the longitudinal layer, and there is little elastic tissue in the wall. Generally there are few or no circular folds in the small intestine, and the jejunum and ileum have little fat in their mesentery.

Large intestine:

At birth this is about 66 cm long and averages 1 cm width. The caecum is relatively smaller than in the adult; it tapers into the vermiform appendix. The ascending colon is shorter in the neonate, due to the shorter lumbar region; the transverse colon is relatively long; the descending colon is short, but twice the length of the ascending colon. The sigmoid colon may be as long as the transverse colon; it often touches the inferior part of the anterior body wall on the left and, in approximately 50% of neonates, part of the sigmoid colon lies in the right iliac fossa. Generally in the colon the muscularis, including the taeniae coli, is poorly developed as in the small intestine. Appendices epiploicae and haustra are not present, giving a smooth external appearance to the colon. Haustra appear within the first 6 month. The rectum is relatively long; its junction with the anal canal forms at nearly right angle.

Meconium:

This is a dark, sticky, viscid substance formed from the passage of amniotic fluid, sloughed cells, digestive enzymes and bile salts along the fetal gut. Meconium becomes increasingly solid as gestation advances but does not usually pass out of the fetal body while in utero. Fetal distress produced by anoxia may induce the premature defection of meconium into the amniotic fluid, causing risk of its inhalation. At birth the colon contains 60-200 g of meconium. The majority of neonates defecate within the first 24 hours after birth ***(Collins, 1995)***.

IV. <u>Physiologic control of the gut blood flow</u>

Pattern of the gastrointestinal blood supply:

The superior mesenteric and inferior mesenteric arteries supply the walls of the small and large intestines by way of an arching arterial system. The celiac artery provides a similar blood supply to the stomach.

On entering the walls of the gut, the arteries branch and send smaller arteries circling in both directions around the gut, with the tips of these arteries meeting on the side of the gut wall opposite the mesenteric attachment. From the circling arteries, still much smaller arteries penetrate into the intestinal wall and spread along the muscle bundles, into the intestinal villi, and into submucosal vessels beneath the epithelium to serve the secretory and absorptive functions of the gut ***(Guyton and Hall, 2000)***.

There is a special organization of the blood flow through an intestinal villus, including a small arteriole and venule that interconnect with a system of multiple looping capillaries. The walls of the arterioles are highly active in controlling villus blood flow ***(Guyton and Hall, 2000)***.

Effect of gut activity and metabolic factors on gastrointestinal blood flow:

The splanchnic circulation accounts for 20% of cardiac output, and at times it may contain one-third of the blood volume. The inferior portion of the duodenum, the whole of the small bowel, and the right half of the colon are supplied by the SMA. The dependence of intestinal blood flow on a single vessel implies that changes in SMA blood flow patterns may have significant physiologic effects on the bowel ***(Crissinger and Granger, 1991)***.

Under normal conditions, the blood flow in each area of the gastrointestinal tract, as well as in each layer of the gut wall, is directly related to the level of the local activity. For instance, during active absorption of nutrients, blood flow in the villi and adjacent regions of the submucosa is increased as much as eight fold or even more at times. Likewise, blood flow in the muscle layers of the intestinal wall increases with increased motor activity in the gut. For instance, after a meal, the motor activity, secretory activity, and absorptive activity all increase; likewise, the blood flow increases greatly but then decreases back to the resting level over another 2 to 4 hours ***(Guyton and Hall, 2000)***.

Possible causes of the increased blood flow during activity:

Intestinal blood flow is regulated by intrinsic and extrinsic mechanisms as well as circulating vasoactive substances. The gastrointestinal tract is the source of a number of neurotransmitters, peptides, and autacoids, and its vascular supply is richly innervated by sympathetic and parasympathetic nerves. The mechanisms that regulate postprandial splanchnic vascular responses in infants, particularly those born prematurely, are unclear. Larger feed volumes and longer intervals between feeds are reported to result in higher relative postprandial SMA blood flow velocity (BFV) ***(Hansen et al., 1998).***

Although the precise cause or causes of the increased blood flow during increased gastrointestinal activity are still unclear, some facts are known.

First, several vasodilator substances are released from the mucosa of the intestinal tract during the digestive process. Most of these are peptide hormones, including cholecystokinin, vasoactive intestinal peptide, gastrin, and secretin. These same hormones control specific motor and secretory activities of the gut.

Second, some of the gastrointestinal glands also release into the gut wall two kinins, kallidin and bradykinin, at the same time that they secrete other substances into the lumen. These kinins are powerful vasodilators that are believed to cause much of the increased mucosal vasodilation that occurs along with secretion.

Third, decreased oxygen concentration in the gut wall can increase intestinal blood flow at least 50 to 100 percent; therefore, the increased mucosal and gut wall metabolic rate during gut activity probably lowers the oxygen concentration enough to cause much of the vasodilation. The decrease in oxygen can also lead to as much as a fourfold increase of adenosine, a well-known vasodilator that could be responsible for much of the increased flow.

Thus, the increased blood flow during increased gastrointestinal activity is probably a combination of many of the fore-mentioned factors plus still others yet undiscovered ***(Guyton and Hall, 2000)***.