CHAPTER I

INTRODUCTION
CHAPTER -I

Introduction

The term ‘Intestinal ischemia’ is used to describe a variety of disorders, all of which ultimately reflect a state of insufficient blood flow to either small intestine, or the colon or both which are collectively referred as the intestine. The superior mesenteric artery, which branches off the aorta, supplies blood to parts of intestine. Blood clot/s in such artery or its branches, cuts off the blood supply to part/s of the intestine. This is known as intestinal ischemia. If this occurs, the intestine may infarct (die). This injury of ‘low-flow’ state can range from a mild bout of short-lived abdominal pain, to a graver situation that may require surgery or possibly lead to death. Acute Mesenteric Ischemia (AMI) may be defined as an abrupt reduction in blood flow to the intestinal circulation of sufficient magnitude to compromise the metabolic requirements and potentially threaten the viability of the affected organs. AMI is a potentially fatal, vascular surgical emergency with an overall mortality rate of 60-80%. AMI comprises a group of pathophysiologic processes that have a common symptom of necrosis.

Over the past two decades it has become clear that the best patient outcomes can be achieved if prompt intervention can be started before widespread necrosis has occurred. However, principal problem with this approach is the lack of a non-invasive, sensitive diagnostic test, which can detect acute ischemia before the development of smooth muscle necrosis\textsuperscript{1,2}.

1.1: Significance of the Study: There are increased incidences of the cases with small bowel infarct. Out of the total abdominal problems 15% cases are reported to be having small bowel ischemia. The progress of the condition is very fast and condition of the patient becomes worse in 4-5 days. Ultimately patient has to undergo for laparotomy in order to confirm the condition and rectification. Even little delay in treatment of the condition results in reperfusion injury. Evenafter such treatment, it may cause irreversible damage to intestine as well as
distal organs further due to generation of free radicals. High survival rate is possible when the condition is detectable in early stage preferably by simple biochemical test. This study will be useful for the detection of intestinal ischemia, a prominent cause responsible for death and help in survival of those patients.

1.2: Blood Supply of the Gut (Human System)

Intestinal blood supply occurs predominantly through three major branches of the abdominal aorta: the Celiac axis, the Superior Mesenteric Artery (SMA), and the Inferior Mesenteric Artery (IMA).

All three vessels originate anteriorly from the aorta, with the celiac axis emerging at a perpendicular angle just under the median arcuate ligament near the level of the diaphragm. The celiac axis is the largest of these arteries, and it trifurcates about 1 to 2 cm beyond its origin into the splenic, the left gastric, and the common hepatic arteries. It is this latter branch that may provide significant collateral flow to the intestine through its first branch, the gastroduodenal artery, as well as the anterior and posterior pancreaticoduodenal arcades. The SMA forms a more acute angle at its origin, which is generally 1 to 3 cm distal to the celiac axis. It courses almost parallel to the aorta proximally before curving toward the right lower quadrant and giving off branches. The IMA is smaller in caliber, originating from the infrarenal aorta, 5 to 8 cm distal to the SMA, and a variable distance from the aortic bifurcation. Other, less common collateral pathways exist as well. A direct connection between the celiac artery and the SMA may be identified on occasion. This represents an embryonic remnant and is known as the arch of Buhler

Extensive collateral circulation exists in the small and large bowel.

Celiac axis and SMA communicate through the pancreaticoduodenal arteries.

SMA and IMA communicate through the marginal artery of Drummond.
IMA gives off superior rectal artery which merges with the middle rectal artery (from internal iliacs) in the rectum.

Celiac axis and its branches supply blood to the stomach, pancreas, spleen, gallbladder and liver.

Superior Mesenteric Artery supplies blood to pancreas, duodenum, jejunum, ileum, ascending and transverse colon.

Inferior Mesenteric Artery supplies blood to supplies distal transverse colon, descending colon, sigmoid colon and rectum. (In case of rat, there is no separate Inferior Mesenteric Artery).

1.3: Pathology:

Intestinal blood flow accounts for 10 to 20% of the resting cardiac output but may, on occasion, exceed 30%. It is widely regulated by a variety of mechanisms, including the autonomic nervous system, a broad array of secreted neurohormonal factors such as gastrin, glucagon, and secretin, as well as other vasoactive peptides such as bradykinin, serotonin, histamine, and the prostaglandins. Of the blood reaching the intestinal wall, most is directed toward the mucosa, the layer with the greatest metabolic demand and highest rate of cell turnover.

A common histopathologic sequence is observed, regardless of anatomic distribution. The earliest ultrastructural changes are noted in the mucosal layer, with alterations observed as soon as 10 minutes after injury in the canine model. Bowel wall edema ensues as a result of loss of capillary integrity. Absence of this natural barrier permits bacterial translocation, promotion of endotoxemia, as well as exudation of fluid into the bowel lumen. The injured mucosa sloughs, leaving ulcerations of the bowel wall.

Although the bowel may still be viable when the mucosa is threatened, prolonged interruption of blood flow ultimately leads to necrosis of the muscularis and serosa, a point at which the compromised segment is no longer
salvageable. Clinically, an already compromised and perhaps frail patient may experience myocardial depression, a progressive inflammatory response with a generalized increase in capillary permeability, resulting in edema and organ dysfunction.

1.4: Risk Factors

Following factors are potential risk factors for occurrence of intestinal ischemia-
- Recently occurred acute Myocardial Ischemia (MI), ventricular aneurysm, and cardiomyopathies. Release of clot can cause blockage of branch/branches of Superior mesenteric artery.
- Atrial fibrillation/flutter
- Hypovolemia or hypotension due to less cardiac output.
- Inherited thrombotic disorders or malignancy
- Pancreatitis
- Hepatitis or cirrhosis
- Age greater than 50

Medication offered for such disorders in general are:

1. Vasopressors
2. Beta-blockers
3. Digoxin
4. Diuretics
Figure 1.1: Blood circulation in Rat.

<table>
<thead>
<tr>
<th>Arterial System</th>
<th>Venous system</th>
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<tr>
<td>Right external common carotid</td>
<td>Right external jugular</td>
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<tr>
<td>Right common carotid</td>
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<td>Right subclavian</td>
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<td>Right axillary</td>
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<td>Thoracoepigastric</td>
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<td>Gastric</td>
<td>Abdominal aorta</td>
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<td>Superior mesenteric</td>
<td>Celiac</td>
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<td>Left internal jugula</td>
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<td>Aortic arch</td>
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| Left axillary | Caudal Vena C.
| Left subclavian | Left renal |
| Left mammary | Caudal |
| Abdominal aorta | Splenic |
| Celiac | Gastric |
| Left renal | Mesenteric |
| Left genital | Right genital |
| Left iliac | Right femoral |

Figure 1.2: Diagrammatic representations of ischemic intestine

(Courtesy: http://www.merck.com/media/mmhe2/figures/fg034_1.gif)
1.5: **Types of Ischemia and pathogenesis:**

In general terms, ischemia can be either localized to a relatively small part of the small intestine or colon, or it may be more widespread and involve significant portions of both (Fig.1.2). The time course of the event may vary as well. It may be acute (new), chronic (long-standing), or pre-existing chronic symptoms may suddenly or gradually worsen. Four physiopathologic phenomenons are present: superior mesenteric artery embolism, superior mesenteric artery thrombosis, non-occlusive acute mesenteric ischemia and superior mesenteric venous thrombosis where the embolism event is most frequent.

**Arterial embolism:** it is the most frequent cause of AMI and responsible for approximately 50% of cases

**Arterial thrombosis:** it accounts for 25-30% of all AMI

**Nonocclusive Mesenteric Ischemia (NOMI):** it accounts for 20% of AMI

**Mesenteric Venous Thrombosis (MVT):** it is the least common type of AMI

1.5.1: **Arterial Embolism**

A blood clot from the heart or main blood vessels may travel through the bloodstream and block one of the arteries supplying the intestine. Typically, the emboli originate in the heart in an akinetic or aneurismal portion of the left ventricle after myocardial infarction, in the left atrium of patients with atrial fibrillation, or, less frequently, in valve cusps harboring vegetations in patients with bacterial endocarditis. Proximal SMA perfusion may be maintained, ensuring viability of the jejunum and resulting in a clear demarcation of the affected intestinal segment at the time of laparotomy. In response to acute occlusion, vasoconstriction may ensue, further compromising arterial perfusion and exacerbating the ischemic injury.
Possible reasons for Arterial embolism:
- Mesenteric emboli originated from a cardiac source after Myocardial Ischemia or recent infarction
- Atrial tachyarrhythmias
- Endocarditis
- Ventricular aneurysms
- Cardiomyopathies

1.5.2: Arterial thrombosis

Atherosclerotic occlusive lesions tend to occur at the origins, or very proximal segments, of the mesenteric arteries. Although the mesenteric arterial circulation is a common location for atherosclerotic occlusive disease among older people, in view of the extensive potential collateral network within the mesenteric circulation, patients with symptoms of chronic mesenteric ischemia are encountered infrequently. Therefore, AMI often develop secondary to acute arterial thrombosis in patients with no prior symptoms suggestive of mesenteric insufficiency. AMI may result from arterial dissection, and most often, this result from extension of an aortic dissection producing the malperfusion syndrome. Less commonly, there may be an isolated dissection of the mesenteric vessel either spontaneously or as a complication of a catheter-based intervention. It is observed clinically that fibromuscular dysplasia and Takayasu’s arteritis may also be associated with an acute mesenteric arterial occlusion. Conversely, arterial thrombosis may occur in vessels with no, or minimal, pre-existing disease secondary to an underlying hypercoagulable state.

1.5.3: Mesenteric Venous thrombosis (MVT):

The primary pathophysiologic process associated with MVT is a rise in portal and superior mesenteric venous pressures. Increased hydrostatic pressure in the intestine leads to luminal fluid sequestration as well as bowel wall edema.
The ensuing relative hypovolemia and hemoconcentration may contribute to vasoconstriction. Ultimately, infarction of the affected intestinal segments may develop. In such cases focal hemorrhage and necrosis lead to loss of the gut barrier function, which ultimately allows for bacterial translocation and possible endotoxemia. The arterial response to MVT may persist well after the venous obstruction has been corrected surgically. MVT is responsible for segmental bowel necrosis with thrombi originating in venous arcades and superior mesenteric vein.

MVT is associated with the following conditions where 75% of patients have thrombotic disorder

- Hypercoagulable states
- Portal hypertension
- Intra-abdominal malignancy
- Pancreatitis
- Abdominal infections
- Blunt abdominal trauma

1.5.4: Non-occlusive mesenteric ischemia (NOMI)

Compromise of intestinal blood flow may occur in the absence of an anatomic arterial occlusion or venous thrombosis as a result of severe mesenteric vasoconstriction. This pathophysiologic mechanism occurs as a manifestation of a shock state due to sepsis, hemorrhage, or cardiac decompensation. It likely represents the disease state similar to ischemic colitis, in which compromise of the blood flow to the left colon is typical state.

Digitalis preparations are generally used to potentiate cardiac contractility in patients associated with NOMI due to arterial and venous smooth muscle contraction. The cocaine, consumed both intranasally and intravenously is responsible in inducing mesenteric ischemia. Affected patients have generally been much younger than the typical population at risk. Occlusive changes in the
mesenteric circulation may develop with prolonged use. Other agents can potentially induce this clinical state by decreasing mesenteric blood flow and promoting vascular smooth muscle contraction include somatostatin, beta-blockers, norepinephrine, and dopamine in high doses.

1.5.5: **Adhesions:**

The intestine can also become trapped in scar tissue from previous surgery (adhesions) and can lead to ischemia if left untreated.

1.6: **Pathological features**

Infarcted bowel is purple, edematous and hemorrhagic. Histologically, transmural necrosis occurs with superficial ulceration and exudation; perforation may occur. In non-transmural ischemia, only the mucosa is affected. Chronic ischemia leads to fibrosis, which can produce stricture.

1.7: **Clinical Manifestation**

‘Pain out of proportion to physical examination is a classic finding.’

Arterial embolism: in this condition acute presentation of severe abdominal pain, nausea, vomiting, and diarrhea (can be bloody) occurs. Due to acute occlusion of vessel and lack of collaterals, symptoms are abrupt.

Arterial thrombosis: here due to slow progressive nature of atherosclerotic disease, patients can develop collateral circulation over time. With thrombosis, patients may not have acute, severe abdominal pain initially but worsen relatively quickly.

In case of Nonocclusive Mesenteric Ischemia acute or subacute symptoms of abdominal pain, nausea, vomiting and diarrhea are usually seen in critically ill patients while in Mesenteric Venous Thrombosis subacute, insidious onset of abdominal pain occurs.
Diagnosis:

The most important symptom of acute mesenteric arterial occlusion, either due to thrombosis or embolism, is severe abdominal pain, which is out of character to the physical findings early in the course of the illness. This apparent inconsistency between the patient’s presenting complaints and the paucity of physical findings, which has clearly been a major factor responsible for delay in establishing the correct diagnosis and poor survival over the years. Vomiting, and less commonly diarrhea, may be seen. Occult blood in the stool and, later, frankly bloody diarrhea are common.

In evaluating the past medical history, evidence of a recent illness, weight loss, changes in eating habits, or postprandial discomfort leading to food aversion may be helpful in differentiating thrombotic from embolic etiologies, although as noted previously, many patients who experience acute mesenteric arterial thrombosis have no symptoms until the acute event. The diagnosis of NOMI is especially difficult because many of these patients are already hospitalized for treatment of other critical illnesses, and initial clinical manifestations of AMI may be masked. Early, the abdomen may be soft, and bowel sounds may be normal. As the ischemic process progresses, there may be guarding, hypoactive or absent bowel sounds with distention and later progressive guarding and peritonitis as full-thickness intestinal necrosis evolves.

Although patients with MVT may have a more protracted and insidious onset of symptoms, once bowel viability is compromised, the physical findings are generally similar to what is seen in the other intestinal ischemic syndromes.

1.8: Laboratory Diagnosis

A complete blood count with differential, electrolyte panel, coagulation studies, liver function tests, and an amylase level should be drawn in any patient suspected of experiencing an acute abdominal process, including AMI. The findings of leukocytosis, acidosis, and elevated amylase level, however, are
consistent with more advanced intestinal ischemia and, most likely, nonviable bowel. Therefore, absence of one or several of these abnormalities should not dissuade the clinician from suspecting the diagnosis of mesenteric ischemia.

Although efforts have been made to establish elevated levels of a number of enzymes, including amylase, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, and mucosal diamine oxidase, as early markers for mesenteric ischemia, all these tests have proved nonspecific and therefore unreliable. It is generally not possible to differentiate the etiology of NOMI from acute arterial thrombosis or embolism on the basis of the laboratory profile, although hemoconcentration, consistent with a generalized dehydration state, is ubiquitous among those experiencing NOMI. Likewise, no specific laboratory test is helpful in identifying the patient with acute MVT, although documentation of a hypercoagulability state may be suggestive.

1.9: Biochemical events in intestinal ischemia and their use in routine clinical practices for diagnosis

Bowel infarction, sepsis, and death may result, making prompt diagnosis and management imperative. Although infarction may occur, colonic ischemia is often a reversible condition with mortality rates considerably lower than those witnessed in acute mesenteric ischemia. Intestinal infarction may represent another example of the multisystem organ failure (MOSF) syndrome. Intestinal ischemia causes delayed neuronal death, which differs from the apoptotic process previously demonstrated in the ischemia-damaged brain. The bowel ischemia and reperfusion may promote gut barrier failure and bacterial translocation, and then contribute to the development of MOSF by allowing bacteria or endotoxin normally contained within the gut to reach the portal and systemic circulations, where it fuels the septic process. Oxygen free radicals, anaphylatoxin, and thromboxane may be potential factors in the development of gut barrier failure.
and MSOF. Overall attempts to diagnose intestinal ischemia in patients have been categorized in two sections namely technique based diagnosis and biochemical diagnosis using physiological samples like blood and urine.

**Technic based parameters for the diagnosis of intestinal ischemia**

Apoptosis is a major mode of cell death in the destruction of small intestinal epithelial cells induced by ischemia and ischemia/reperfusion injury. Disruption of epithelial cell-matrix interactions (‘anoikis’) may play an important part in induction of apoptosis in detached enterocytes. The Basic Electrical Rhythm (BER) of the intestine is known to decrease during mesenteric ischemia. Microscopic examination of the biopsies revealed evidence of progressive infarction of the mucosa during ischemia. There was an acute worsening of the pathology during reperfusion, the severity being greater when reperfusion was preceded by longer periods of ischemia. These changes were statistically significant. Reperfusion injury is reflected in the histopathologic response and that this is worse in severity than the response to ischemia.

The BER of the small intestine can be measured noninvasively using a Superconducting Quantum Interference Device (SQUID). The SQUID magnetometer is a reliable noncontact device that can detect early intestinal ischemia in animal models. It is believed that further technical developments will permit the noninvasive diagnosis of mesenteric ischemia.

The intestinal mucosa is composed of multiple barriers to the lumen-to-blood transport of solutes, including the unstirred water and mucous layers, the apical and basolateral cell membranes of the epithelial cell, the paracellular junctions, the interstitial matrix, and the capillary and lymphatic endothelia. The epithelial barrier appears effectively to restrict the movement of solutes with a radius as low as 3 Å, yet it also permits limited permeation by molecules as large as albumin (36 Å radius). There is evidence to suggest that the restrictive properties of the gastrointestinal mucosa are significantly altered under various
physiological and pathological conditions, and measurement of plasma (or luminal) clearances of water-soluble molecules has proved to be a popular method for studying intestinal permeability\textsuperscript{12}.

Computed Tomography (CT) can demonstrate changes because of ischemic bowel accurately, may be helpful in determining the primary cause of ischemia and can demonstrate important coexistent findings or complications. However, common CT findings in acute small bowel ischemia are not specific and therefore, it is often a combination of clinical, laboratory and radiologic signs that may lead to a correct diagnosis\textsuperscript{13}. Various scholars understand and recommend that examination should be performed with intravenous contrast administration and thinner sections and multi-planer image reformation to evaluate a site of particular interest. Their observations say that CT also provides characteristic findings indicating the presence of closed-loop obstruction and intestinal ischemia, which leads to appropriate and timely management for these emergent case\textsuperscript{14-22}. Although some of the CT features overlap, a short segment involvement with wall thickening of 1 cm or greater is typical of intramural hemorrhage; a long segment involvement with wall thickening of less than 1 cm is typical of ischemia\textsuperscript{23}.

Rapid, noninvasive imaging strategies, especially multidetector spiral CT and CT Angiography (CTA) as well as gadolinium-enhanced MR Angiography (MRA), have facilitated early diagnosis of splanchnic venous thrombosis, a potentially lethal cause of intestinal ischemia\textsuperscript{24}. According to Kim et al\textsuperscript{25} MR imaging was nearly equal to CT for detecting intraluminal or peritoneal masses, lesions in the bowel and mesentery and small bowel obstruction, but was definitely inferior for detecting omental lesions. The most successful MR imaging sequence was HASTE for demonstrating bowel wall thickening, coronal FLASH 2D for mesenteric lesions and axial FLASH 2D for omental lesions. Helical CT is a highly sensitive method to diagnose or rule out intestinal
ischemia in the context of acute small-bowel obstruction. CT and MR imaging have an important role in establishing the diagnosis of mesenteric ischemia.

However, without specific signs such as thromboembolism in the mesenteric vessel, intramural or portal venous gas and the absence of bowel wall enhancement, mesenteric ischemia can be confused with inflammatory or neoplastic gastrointestinal diseases. Experimental intestinal ischemia was reliably detected by bladder opacification after administration of enteric contrast. CT detection of systemic absorption of enteric iohexol was more sensitive than plain film radiographs and may be useful in the diagnosis of intestinal ischemia, although it may not be specific for ischemia. According to Frager et al, CT is a sensitive but not completely specific preoperative indicator of intestinal ischemia in patients with small-bowel obstruction due to hernias or adhesions. Absence of CT findings of ischemia or infarction does not rule out strangulation.

If clinically suspected, the diagnostic procedures such as duplex sonography and arterial angiography should be carried out immediately. Although the diagnosis is often quickly clear, perioperative mortality rate remains high. Even though the duplex sonography often confirms the diagnosis with high accuracy, the angiography remains the diagnostic gold standard. Technique like Laser Doppler Flowmetry (LDF) is a sensitive guide and feasible method to evaluate and define the viability of ischemically injured intestine. Photoplethysmography is the preferred method of assessing intestinal viability in the presence of ischemia, while studying the ischemic injury of bowel the LDF and tissue oximetry (TP02) as predictors of the development of bowel necrosis were attempted.

Non-invasive tests for evaluation of intestinal blood flow include duplex scanning and LDF have been accepted earlier. The most important trends in the diagnosis and management of chronic intestinal ischemia include: increasing use of duplex ultrasound scanning in the initial evaluation of patients with
possible intestinal angina, rapidly evolving noninvasive clinical tests to assess mucosal perfusion (reflectance spectrophotometry, LDF and tonometry), and preferential use of antegrade mesenteric grafts or transaortic endarterectomy for mesenteric atherosclerotic occlusive disease. Though the sensitivity of Doppler ultrasound is significantly less than that of laser Doppler and perfusion fluorometry, the latter two techniques are more quantitative. Doppler ultrasound promises to be more accurate than conventional ultrasound in the diagnosis of visceral ischemia and may help to identify those patients who may require angiography. NCLBF (non-contact Laser tissue Blood Flowmeter) is useful to assess intestinal viability, suggesting the possibility of clinical use. Application of abdominal phonoangiography in patients with suspected chronic intestinal ischemia may be diagnostic or highly suggestive of vascular compromise.

The viability of rat intestinal loops was assessed by three methods: on clinical basis, by detection of reactive hyperemia using an electronic thermometer, and by intra-arterial dye injection. The intra-arterial dye injection method proved to be a simple, easy and inexpensive way to accurately predict the viability of ischemic rat intestine. The laparoscopic use of ultraviolet light combined with intravenous fluorescein dye is an effective diagnostic tool for evaluating mesenteric ischemia in pigs. The data from the above mentioned preliminary study demonstrate that proton magnetic resonance imaging may be used to discriminate between ischemic and nonischemic small intestine.

Technique like MR imaging with polylysine-Gd-DTPA enhancement can detect acute occlusive ischemia of the rat intestine at an early stage. Also technique like Tc-99m HMPAO leukocyte scintigraphy may be helpful in the noninvasive diagnosis of ischemic injury to the colon, especially after aortic graft surgery. The results showed that experimental small-bowel infarction can be detected as early as five hours after the onset of ischemia. Because most laboratory and radiologic studies are nonspecific in early ischemia, aggressive
approaches to diagnosis with imaging of the splanchnic vasculature by mesenteric angiography is advocated\textsuperscript{65}.

**The Biochemical diagnosis using physiological samples like serum and urine**

Continuous monitoring of glucose, lactate, and glycerol using a microdialysis technique was performed. A significant increase of microdialysate lactate and a significant decrease of microdialysate glucose were found during occlusive ischemia as compared to the preischemic samples and samples from the nonischemic control catheters. Here the microdialysate glycerol was found to be increased during ischemia, but later than the lactate\textsuperscript{66}. The changes of plasma D(-)-lactate levels in systemic blood was found paralleled with LPS levels in the portal vein blood. The measurement of plasma D(-)-lactate level may be a useful marker to assess the intestinal injury and to monitor an increase of intestinal permeability and endotoxemia following severe injuries in early stage\textsuperscript{67,68}.

Concentrations of intestinal glucose, succinate, lactate, amino acids, phosphocholine (PC), glycerophosphocholine (GPC), choline, and phosphoenergetics were measured by various researchers using magnetic resonance spectroscopy of freeze-clamped small intestinal extracts. Intestinal ischemia alone caused a significant drop in glucose and phosphoenergetics but caused an increase in amino acids, succinate, and lactate. Ischemia and ischemia-reperfusion decreased PC and GPC but increased choline\textsuperscript{69-79}.

Spectrophotometric NBT assay is an accurate technique for quantitating small intestinal ischemic injury, which also gives useful information about the functional status of mitochondria\textsuperscript{80}. Cellular retinol binding protein II (CRBP-II) and intestinal fatty acid binding protein (I-FABP) are both expressed in small intestinal enterocytes\textsuperscript{81}. Intestinal fatty acid binding protein (FABP), a cytosolic protein uniquely located in mature small intestinal enterocytes has been shown to be a sensitive biochemical marker of early intestinal ischemia when assayed in urine. Urine intestinal FABP was 100\% sensitive and 92 \% specific w.r.t. GI
tract complication and can be used as useful marker. In this research Intestinal fatty acid binding protein (I-FABP) immediately appeared in the serum (within 15 min.) on reperfusion with segmental arterial ligation. Urinary content of I-FABP rose 60 min. after its initial appearance in the serum.

Serum hexosaminidase and lactate dehydrogenase levels only increased after 3 hrs of SMA occlusion with reperfusion. Preliminary findings suggest that hI-FABP may serve as a diagnostic marker for early intestinal mucosal compromise and in addition, that it should prove useful as a tool in developing rationale therapeutic regimens to treat these complex clinical problems. The serum concentration of cytosolic beta-glucosidase (CBG), an enzyme found primarily in enterocytes, is markedly elevated in animal models of ischemia and bowel obstruction. In the guinea pig model, cytosolic beta-glucosidase (CBG) was found to be a sensitive marker of ischemic injury caused by arterial occlusion or closed-loop obstruction of the small bowel.

Creatine kinase (CK; EC 2.7.3.2) has three isozymes (CK-MM, CK-MB and CK-BB) in cytoplasm and two isozymes (non-sarcomeric and sarcomeric) in mitochondria. CK-MB is measured either by enzyme activity or mass concentration and is measured as a marker not only in the diagnosis of AMI but also in suspected AMI and unstable angina. The results suggest that plasma lactic acid (LA) and peritoneal LA are sensitive indicators in the early diagnosis of bowel ischemia.

The determination of both serum and peritoneal Xanthine Oxidase (XO) and inorganic Phosphate (iP) were also helpful for early diagnosis of intestinal ischemia; in contrast, serum CK was not a useful indicator. Xanthine oxidase is thought to be the major source of free radicals in the small intestine. During ischemia ATP is catabolized to hypoxanthine, which is enzymatically transformed to xanthine, a process generating oxygen free radicals. ATP content is marker of tissue injury. Decrease in intestinal ATP content after 120min. of ischemia was observed and reported by Schmeling et al.
Moreover oxygen free radicals seems to be produced by activated neutrophilic granulocytes. The serum MDA levels are valuable markers of diagnosis in intestinal ischemia\(^9\). Plasma aspartate aminotransferase (AST) showed a significant increase during reperfusion while Lactate Dehydrogenase (LDH) and creatine kinase levels were significantly increased at the end of ischemia and continued to be so throughout reperfusion. It is difficult to claim that enzymes arise from the intestine, but an increase of CK, LDH, and later of AST without any increase in alanine aminotransferase levels during ischemia suggests that their primary source is the injured intestine\(^9\).

In some cases serum interleukin-6 levels were significantly increased in patients with acute intestinal ischemia\(^9\). A threshold of 4 ng/ml for alpha GST was 100 per cent sensitive and 86 per cent specific for AMI. It is observed that a normal alpha-GST and WBC may exclude the presence of AMI\(^9\). The ammonia level in the blood could be used as a good early indicator of acute mesenteric ischemia\(^9\). Serum phosphate level independently has no diagnostic or prognostic value in acute ischemic bowel disease\(^10\)-\(^16\). There was an increase in plasma insulin level after ischemia. Plasma amylin concentration is related to the severity of intestinal ischemic injury\(^10\).

Decreased DAO activity has been shown to be correlated with the extent of histologic injury. Serum level of the intestinal enzyme Diamine Oxidase (DAO) was studied approximately 24 hr after the onset of symptoms, and was found to be 7.4 times above the normal value. Intestinal ischemia is associated with decreased intestinal DAO activity, which is influenced by the mechanism and duration of intestinal ischemia\(^10\)-\(^11\). The lysosomal acid hydrolase, hexosaminidase (HEX), is known to be elevated in intestinal infarction. Serum HEX activity may be a good marker for intestinal gangrene in neonates with necrotizing enterocolitis\(^11\).

Breath hydrogen measurements appear to reflect functional (hemorrhagic shock-induced) and mechanical (vascular occlusion induced) enteric ischemia in
dogs. Similarly one-hour intestinal ischemia by clamping the superior mesenteric artery and interrupting the intramural collaterals was demonstrated that limulus-positive substances escape from the intestine both via the lymph and blood. Intestinal ischemia and reperfusion leads to significant increases of the circulating TNF-alpha and IL-6 activities, depending on the duration of the ischemia phase, in the absence of detectable endotoxin in the circulation. Occlusion of the SMA induced significant decreases in pHi and intestinal blood flow (IBF). Arterial and portal venous blood gas analyses were less sensitive than tonometric measurements of pHi and there was no correlation between results of blood gas analyses and tonometric measurements.

Histologic score for intestinal mucosal injury increased significantly, depending on duration of ischemia and there was a correlation between tonometric results and the histologic score. Superior Mesenteric Artery (SMA) occlusion followed by reperfusion (I/R) injury caused gastric surface epithelial cell injury and significantly increased serum and antral gastric levels of cytokines. Regional PCO$_2$ (Pr CO$_2$) increased significantly in the intestinal region, in the small intestine, only during the SMA clamping. PAH plasma-to-lumen clearance is a feasible, reliable and inexpensive method for the evaluation of ischemia/reperfusion injury to the intestinal mucosa. It can safely replace the commonly used method in animal models that utilizes radioactive materials such as $^{51}$Cr-EDTA.

Low levels of endotoxin were detected in plasma following hemorrhage, indicating that intestinal ischemia results in low levels of LPS leaking into the circulation. Measuring iodine levels in serum or urine may be helpful in the evaluation of the degree of mucosal injury induced by intestinal ischemia. Intravenously administered fluorescein sodium (FSC) has long been used intraoperatively to assess bowel viability because its uptake is inversely proportional to the degree of intestinal ischemia. FSC endoscopy appears to be a sensitive and accurate method for detecting and monitoring ischemic colitis and...
has many potential clinical applications\textsuperscript{123}. The intraperitoneal use of 133Xe therefore continues to show promise for the recognition of patients with early intestinal ischemia. Quantitative fluorescence was determined with a perfusion fluorometer after an intravenous bolus of fluorescein\textsuperscript{124}. In an interesting experiment Qualitative fluorescence was determined by examination under a Wood's lamp in a darkened room. The visual fluorescence is not reliable in assessing intestinal viability in early revascularization after arterial occlusion, but quantitative fluorometric fluorescence is reliable in almost all instances\textsuperscript{125}.

Inspite of all these efforts and suggestive parameters, diagnosis of intestinal ischemia is still challenge due to lack of sensitivity, specificity and feasibility of those parameters to use them in routine clinical practices. This study mainly focuses to find out biochemical or technique based parameter/s which will help in diagnosing intestinal ischemia either alone or along with already suggested parameters.