# SECTION I - PATHOPHYSIOLOGY

## HEPATIC BLOOD SUPPLY

The liver is the largest discrete organ in the human body, occupying 2% of the total body weight (1). As an intra-abdominal organ, the liver is the last link in the much larger splanchnic system. Basic hepatic functions include vascular storage and filtration, secretion of bile, metabolism and synthetic activity (2).

### Splanchnic Circulation

The splanchnic organs include the large and small intestine, pancreas and spleen. These are an integrated intra-abdominal system that receives blood from the celiac, superior and inferior mesenteric arteries. This system receives an average of 25% of the total cardiac output (2). The capacitance of the system is large and usually holds 30% of the estimated blood volume under normal conditions (1). The liver by itself may contain 10% of the estimated blood volume. Under the influence of the sympathetic nervous system, the liver can extrude 5OOcc of blood acutely into the circulation (1).

The hepatic bed has a dual blood supply consisting of the portal vein and hepatic artery (3). The portal vein is a product of the confluence of venous drainage from the splanchnic organs. These include the splenic, superior and inferior mesenteric veins. The hepatic artery is a direct branch of the celiac artery.

Although the portal vein supplies up to 75% of the total hepatic blood flow, only 45-55% of the oxygen requirements are provided by this part of the circulation (4). Instead, hepatic artery, which only supplies 25% of total hepatic blood flow delivers up to 45-55% of the oxygen requirements (4,5). Together, the dual vascular supply provides the total hepatic oxygen requirement and a small reserve. Certain zones, which are distant to the main blood vessels, have minimal oxygen reserve and are predisposed to ischemic injury (3).

### Hepatic Reserve

It is well known that the liver has impressive functional reserve. This is easily appreciated after hemihepatectomy in patients with mass lesions as there is usually no impairment in physiological function postoperatively. Furthermore, regenerative properties of the liver are well documented (4). A hepatocyte is capable of recovery up to the point of mitochondrial damage, while an acinus can regenerate if a single layer of cells adjacent to the hepatic arteriole survives (6).

Hepatic function is protected by autoregulation of splanchnic blood flow. Both intrinsic and extrinsic mechanisms control blood and oxygen supply. Control of total hepatic blood flow within the liver has three different aspects. Regulation occurs through: 1.) hepatic arterial, 2.) portal venous flow and 3.) the interrelationship between these circuits (7). These responses in the liver are less efficient than in other organ systems. A pressure-flow relationship is the basis for hepatic arterial regulation (8). The liver differs from other systems, however, in that autoregulation primarily occurs in the metabolically active (postprandial) state (8).

In contrast, venous blood delivery to the portal bed is passive and is controlled by the extrahepatic splanchnic circulation (8,9). Both metabolic and neurogenic mechanisms have been identified as factors controlling mesenteric and splenic blood flow (7). Portal pressure is the regulated variable rather than venous blood flow. This is opposite to most other autoregulated systems (7). In other words, portal venous pressure and not flow is the factor that is kept constant. Extrinsic regulation of the splanchnic bed is mediated through autonomic and catecholamine stimulation of all splanchnic organs in response to metabolic and hemodynamic demands.

The interaction between the hepatic arterial and portal venous vascular beds has been termed "reciprocity" (10). This describes the reciprocal relationship between flow and resistance in arterial and venous supply. Reduction of flow in the portal vein decreases hepatic arterial resistance and consequently increases arterial blood flow. Reduction of arterial flow lowers portal resistance, however, does not directly alter flow. Instead, the latter is regulated by the prehepatic splanchnic vasculature. Studies on hepatic reciprocity have shown that it is an intrinsic response and not dependent on liver innervation (8). Complete occlusion of one circuit reduces vascular resistance in the other by up to

20% (11). In spite of these compensatory changes in the hepatic blood flow, single circuit occlusion in most normal individuals results in insufficient oxygen delivery and complete hepatic failure usually ensues (11).

## RISK ASSESSMENT

## HEPATIC DISEASE AND RISK

Due to the large reserve of the liver, significant impairment of physiological function must occur before clinical signs and symptoms of hepatic failure become evident. However actual functional impairment may exist at earlier stages in the natural history of the disease that consequently place the liver at higher risk of subsequent injury. There is increased risk of toxic and ischemic damage due to the decreased hepatic reserve. With these attendant problems, alterations in splanchnic blood flow or changes in pressure-resistance relationships within the liver may generate recurrent hepatocellular injury.

Both anesthesia and surgery may play a role in hepatocellular injury (12,13). Regional and general anesthesia can cause circulatory changes that can reduce vital blood flow to the liver (12,13). Furthermore, some intravenous and inhalation anesthetics agents may produce widespread toxic damage within a compromised liver (14). Simple surgical manipulation can challenge the relatively weak autoregulatory capabilities of the hepatic bed.

The concept of increased risk in underlying hepatic disease as presented above is an important consideration since it forms the basis for preventative management. Issues that follow from this relate to identification, quantification and assessment of the patient at risk. These topics will be dealt with briefly in the following discussion.

### Identification of the Patient at Risk

Patients that have hepatic impairment and are at increased risk of further injury may be difficult to identify during preoperative assessment. Risk factors and symptoms of liver impairment are not as well defined as in other organ systems. Also, signs of end organ damage are often not apparent until late in the course of the disease. This leaves the anesthesiologist with a poor means of screening by history and physical examination. At the same time we know that 1/700 asymptomatic patients admitted for elective surgery have unexplained abnormalities in liver function tests during routine pre-operative evaluation (1 5). One third of these patients experience an episode of jaundice over the next two weeks. Other studies have confirmed at least a 0.135% incidence of significant liver disease in completely asymptomatic patients presenting for elective surgery (16). Patients with cirrhosis have twice the incidence of cholelithiasis (17). Identification of these patients may result in a change of anesthetic or surgical plan depending on the nature of the nature of the underlying illness. There is, however, no easy means of reliable identification or screening.

### Degree of Risk

There is little doubt that intra-abdominal surgery in the presence of hepatic disease is associated with increased morbidity and mortality. It is well known that hepatic failure is second only to coronary artery disease as a cause of death following cholecystectomy (17). In a study from Britain of patients that had unsuspected liver disease at the time of laparotomy, the morbidity and mortality within one month of operation was 61 and 31 % respectively (18). All patients with acute viral or alcoholic hepatitis died.

To date, risk assessment has been primarily performed in patients with known liver disease and the quantification of risk in asymptomatic patients can only be extrapolated from these studies. Table I illustrates the averaged risk in patients with varying degrees of hepatic impairment secondary to cirrhosis undergoing cholecystectomy (l9). This is in comparison to a control mortality rate of less than 0.5%.

| Table 1. REVIEW OF LITERATURE | | | | |
|---|---|---|---|---|
| Source/ Year | No. Of Patients | Mortality % | Morbidity % | Requiting Transfusion (%) |
| Schwartz 1981 | 21 | 9.5 | 4.8 | 61.9 |
| Aranha, et al. 1982 | 55 | 25.5 | 23.6 | 42.6 |
| Castaing, et al. 1983 | 14 | 7.5 | 7.1 | |
| Manfredi, et al. 1983 | 19 | 21 | 25 | |
| Garrison, et al. 1984 | 39 | 20.5 | | |
| Present Study | 49 | 10.2 | 12.2 | 44.9 |

Further analysis of this problem is shown in Table 2. In this review specific risk factors have been identified that appear in cases associated with increased morbidity and mortality (20). Low albumin and prolonged PT, which indicates markedly impaired synthetic ability, were associated with increased risk. In addition, abnormalities in serum bilirubin and bromsulphalein excretion also correlate with poor outcome. Emergency surgery was the most impressive predictor of poor outcome in this study.

| Table 2. STUDIES OF NONPORTOSYSTEMIC SHUNT SURGICAL RISK IN PATIENTS WITH CIRRHOSIS | | | | | | |
|---|---|---|---|---|---|---|
| INVESTIGATOR | No. Of PTS | INDICATION FOR SURGERY | CAUSE OF CIRRHOSIS | MORTALITY RATE | MORBIDITY RATE | RISK FACTORS |
| Guyer (1955) | 35 | Mostly abdominal | NS | 19% | NS | Low albumin, anemia, prolonged PT, ascites |
| Lindenmoth (1963) | 104 | Mixed | NS | 7% | 25% | BSP>10%, albumin <3 gm per dl |
| Wirthlin (1974) | 83 | Nonvariceal gastroduodenal bleeding | NS | 57% (emergency) 8% (elective) | NS | Emergency surgery, bilirubin >2 mg per dl, albumin <3gm per dl, PT > 16 sec. elevated ammonia |
| Schwartz (1981) | 33 | Biliary | Mixed | 15% | 39% | Bile duct obstruction |
| Aranha (1983) | 55 | Biliary | Alcoholic | 9% PT ≤ 2.5 sec. pro-longed; 83% PT >2.5 sec | 26% 17% | Prolonged PT |
| Doberneck (1983) | 102 | Mixed | NS | prolonged 20% | 47%a | Bilirubin > 3.5 mg per dl, alkaline phosphates > 70 IV. PT >2 see prolonged Gastrointest. surg.ascites, emer. surg., Operative blood loss > 1000 ml postop com-plication |

The Child scoring system, shown below (Table 3), documents the degree of hepatic impairment in individual patients. The system was originally designed to risk stratify patients undergoing porto-systemic shunting procedure. Using this method mortality rates of 10%, 31% and 76% were identified in Child class A, B, and C patients respectively (21). Subsequently, it has gained wide use as a basis for risk assessment and long-term prognosis. This scoring system has been tested on patient populations and found to have reasonable predictive value for operative outcome and estimated blood loss.

| Table 3. CLINICAL AND LABORATORY CLASSIFICATION OF PATIENTS WITH CIRRHOSIS IN TERMS OF HEPATIC FUNCTIONAL RESERVE (Data from Child 1964) | | | |
|---|---|---|---|
| | GROUP A | GROUP B | GROUP C |
| Serum bilirubin ($\mu$mol litre$^{-1}$) | < 40 | 40-50 | > 50 |
| Serum albumin (g litre$^{-1}$) | > 35 | 30-35 | < 40 |
| Ascites | None | Easily controlled | Poorly controlled |
| Neurological Disorder | None | Minimal | Advanced coma |
| Nutrition | Excellent | Good | Poor-wasting |
| Risk of Operation | Good | Moderate | Poor |

**The Pugh scoring system (Table 4) is a modification of the original Child classification where prothrombin time has been substituted for nutritional status (21). The latter substitution has improved predictive value. Numerical scores can be assigned which gives quantitative index of risk, similar to the cardiac Goldman classification. Overall, only Child Class A (Pugh 5-6) are considered a reasonable risk for intra abdominal surgery.**

| Table 4. GRADING OF SEVERITY OF LIVER DISEASE (Data from Pugh and others, 1973) | | | |
|---|---|---|---|
| Clinical and Biochemical Measurement | Points Scored for Increasing Abnormalities | | |
| | 1 | 2 | 3 |
| Encephalopathy (grade) | None | 1and 2 | 3 and 4 |
| Bilirubin ($\mu$mol litre$^{-1}$) | .< 25 | 25-40 | > 40 |
| Albumin (g litre$^{-1}$) | 35 | 28-35 | < 28 |
| Prothrombin time (seconds prolonged | I-4 | 4-6 | > 6 |

## HEPATIC ASSESSMENT

As mentioned previously, clinical evidence of hepatic disease is often not apparent until late in the course of the illness. Furthermore, the clinical problems associated with liver insufficiency are relatively nonspecific on history and physical exam. Despite these limitations there are clinical scenarios that should raise suspicion of underlying liver disease. Information regarding family history, inflammatory bowel disease, environmental exposure and alcohol consumption should be obtained as well any contact with known infected *individuals, prior* transfusion, tattoos and ingestion of potential hepatotoxins. This knowledge together with a description of clinical symptoms can help in identifying hepatic impairment.

Liver function tests can measure different aspects of hepatic function. As a group of tests, they lack specificity and are often affected by non hepatic function (6). Quantification of hepatic impairment is not obtained from a single set of tests. Consequently, results need to be interpreted in the total clinical context. These observations are not indicative of good screening tests.

Common biochemical markers used in the evaluation of hepatobiliary function consist of serum bilirubin, enzymes, proteins and coagulation profile. Since serum enzymes are frequently used as diagnostic indicators, their role and limitations will be briefly *discussed.*

The cytosolic aminotransferases consists of AST (aspartate aminotransferase) and ALT (alanine aminotransferase). Elevation of AST is caused by damage to hepatocytes, myocardium or skeletal muscle. ALT is more hepto specific, reflecting cell membrane damage and necrosis. In the absence of myocardial or muscle injury, high levels of serum transaminases suggest hepatocellular injury. Moderate elevations (2-20X normal) are often seen in anicteric or subclinical viral hepatitis. High values occur in severe acute viral or toxic hepatitis. Low to normal levels of serum enzymes may be observed in chronic hepatocellular destruction, complete liver failure and cholestatic disease. Alkaline phosphatase (ALP), a membrane bound enzyme, is produced by many tissues and is excreted in the bile. In hepatobiliary disease, enzyme synthesis increases and there is a large release of ALP into the bloodstream. In the absence of bone disease and pregnancy, an elevated ALP reflects impaired biliary function. Slight to moderate increases in ALP occur in all types of liver disease. The most striking elevations (IOX normal) occur in extra or intrahepatic cholestasis.

A sensitive indicator of hepatocellular and renal damage is gamma-glutamyl transpeptidase (GGT). GGT is elevated in the serum of virtually all patients with cellular liver damage. Significantly raised levels are usually observed in acute hepatic injury before other liver function tests show abnormalities. Similar to ALP, 5'nudeotidase is a hepatobiliary enzyme. It is relatively specific but insensitive indicator of cholestasis. It is very useful in equivocal elevations of the ALP. Changes in serum albumin and coagulation parameters are *considered late* signs of liver disease and are primarily used to mark the severity of hepatic impairment.

The diagnosis of liver disease requires a high degree of suspicion and a careful probing of the clinical history. Biochemical tests add to the accuracy of diagnosis. In contrast, anesthesiologists are often confronted with abnormal hepatic function tests in asymptomatic patients. Some of these abnormalities may be secondary to the surgical illness or coexisting liver disease. Patients with underlying hepatic impairment are important to identify since they are at increased risk for further injury due to alterations in splanchnic blood flow, which occurs during anesthesia and intra-abdominal surgery. Medical management of these patients may be changed if liver disease is identified.

The question of whether further investigation should be pursued in all cases of subtle changes in liver function tests is widely debated (15,19,20). Most authors agree that the clinical history must be examined closely and that any findings associated with liver disease be investigated. Misinterpretation of liver function tests is, however, a problem that may result in a failure to recognize primary hepatic impairment (17). Inability to distinguish hepatocellular injury from cholestatic patterns has been identified as a recurring mistake. This alone may lead to an incorrect diagnosis and inappropriate treatment.

Further controversy exists over the use of liver function tests as a screening tool in patients undergoing intra-abdominal surgery (6,16,20). Some studies have supported the use of screening in such patient populations, showing the fortuitous diagnosis of liver disease, which either led to an appropriate cancellation of the procedure or an alteration in anesthetic technique.

The disposition of a patient presenting for surgery with a previous history of jaundice also poses a special dilemma for the anesthesiologist. Clinical history can be very helpful in establishing a differential diagnosis. But again, whether these patients should undergo further investigations is controversial depending on the clinical history. Current literature favors the review of liver function tests in these patients (20,21).

In summary, the liver, which is the largest organ in the body, is an integral part of the splanchnic system. Although there is a dual blood supply, oxygen delivery is highly dependent on hepatic arterial blood flow. Reciprocity of flow occurs between the hepatic arterial and portal venous circuits but there is incomplete compensation with hepatic necrosis often occurring after the interruption of arterial flow. A pressure-flow relationship has been identified for hepatic arterial supply in the postprandial liver but this response is not as well defined as in other organ systems. Portal flow is controlled primarily by extrahepatic factors to maintain a constant pressure gradient. This results in a weak autoregulatory response to alterations in cellular demands and places the liver at increased risk of ischemic injury.

Both anesthesia and surgery may impair liver function through alterations in splanchnic flow or toxic injury. Hepatocellular failure may occur post-operatively in patients that present for intra-abdominal surgery with decreased hepatic reserve. Furthermore, there is a direct correlation between the severity of liver disease and the resulting morbidity and mortality. A good predictor of outcome is the Child or Child-Pugh classification. Patients who have liver disease, however, are not always easily identified due to the nonspecific nature of the signs and symptoms.

Liver function tests have been found to be useful in the diagnosis of hepatic disease when interpreted in the clinical context. The use of these tests for screening is widely debated. Some investigators suggest the routine use of liver function tests on all patients undergoing intra-abdominal surgery since this population is at increased risk. The lack of specificity of these tests results in a problem of interpretation in the asymptomatic patient. The decision to further investigate the latter group of patients is, therefore difficult. Incorrect interpretation of liver function tests has resulted in failure to recognize hepatocellular compromise that will affect management and outcome. Continuing education on the topic of pre-operative liver function test may prevent this problem.

The preoperative management of the asymptomatic patient with a prior history of jaundice has also been debated. Most authors agree that these patients warrant further probing into the clinical history and evaluation by screening with liver function tests. Any risk factors or diseases states associated with abnormal hepatic function should be identified.

Patients with liver disease are not always easily identified by brief clinical examination. There is at least a 0.135% incidence of significant hepatic impairment in asymptomatic patients that present for elective surgery. A thorough understanding of assessment and identification of the patient at risk will lend guidance to the use and interpretation liver function tests as part of a rational clinical approach.

**REFERENCES**


1 Lautt WW and Greenway C: Hepatic venous compliance and role of liver as a blood reservoir Am. J. Physiol. 1976;231:292-295

2. Guyton AC: The Liver as an Organ. Textbook of Medical Physiology (8th ed). WB Saunders Co., Philadelphia, 1991;771-788

3. Maze M: Hepatic Physiology (3rd ed) in Anesthesia ed by Miller. Churchill Livingstone, New York, 1990;585- 600

4. Gelman S: Anesthesia and the Liver in Management of Anesthesia ed by Barash. JB Lippincott Co., Philadelphia, 1989;1133-1162

5. Cooperman LH: Effects of anesthetics on the splanchnic circulation. Br. J. Anaesth 1972;44:967-970

6. Gornall AG, Goldberg DM: Hepatobiliary disorders. Applied Biochemistry of Clinical Disorders. Harper and Row Publishers, Philadelphia, 1980;164-192

7. Richardson PD, Withrington PG: Liver Blood Flow I. Intrinsic and nervous control of liver blood flow. Gastroenterology 1981;81:159-173

8. Hanson KM, Johnson PC: Local control of hepatic arterial and portal venous flow in the dog. Am. J. Physiol. 1966;211:712-720

9. Richardson PD, Withrington PG: Pressure-flow relationships and effects of noradrenalin and isoprenaline on the hepatic arterial and portal venous vascular beds of the dog. J. Physiol. 1978;282:451-470

10. Hirsch LJ, Ayabe T, Glick G: direct effects of various catecholamines on liver circulation in dogs. Am. J. Physiol. 1976;230:1394-1399

11. Kim DK, Kinne DW and Fortner JG: Occlusion of the hepatic artery in man. Surg. Gynecol. Obstet 1973;136:966-968

12. Gelman S. Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia, Anesthesiology 1984;61:726-730

13. Kennedy WF, Everett GB, Cobb LA, Allen GD: Anesth. Analg. 1970;49:1016-1022

14. Kenna JG and Van Pelt FN The metabolism and toxicity of inhaled anesthetic agents. Anesth Pharmacol Rev. 1994;2:29-42

15. Schemel WH: Unexpected hepatic dysfunction found by multiple laboratory screening Anesth. Analg. 1976;55:1810-1812

16. Wataneeyawech M, Kelly KA: Hepatic diseases unsuspected before surgery N.Y. State J. Med. 1975;1278-1281

17. Bloch RS, Allaben RD, Walt AJ: Cholecystectomy in patients with cirrhosis Arch. Surg. 1985;120:669-672

18. Powell-Jackson P, Greenway B, Williams R: Adverse effects of exploratory laparotomy in patients with unsuspected liver disease Br. J. Surg. 1982;69:449-451

19. Garrison RN, Cryer HM, Howard DA, Polk HC: Clarification of risk factors for abdominal operations in patients with cirrhosis Ann. Surg. 1984;199:648-655

20. Friedman LS, Maddrey WC: Surgery in the patient with liver disease Med. Clin N.A. 1987;71:453-476

21. Strunin L: Preoperative assessment of the patient with liver dysfunction Br. J. Anaesth. 1978;50:25-31

## THE DIFFERENTIAL DIAGNOSIS OF POSTOPERATIVE JAUNDICE

The development of jaundice in the postoperative period indicates significant physiological dysfunction. Mechanisms underlying abnormal bilirubin metabolism are complex and usually multifactorial in this setting. Anesthesiologists are often asked to help in the assessment of these patients so that an etiology can be identified. Therefore the following approach to the differential diagnosis of jaundice in the postoperative patient is briefly outlined.

### Unconjugated Bilirubin

The first step is to differentiate conjugated from unconjugated bilirubin. Unconjugated hyperbilirubinemia is defined as an elevation of the serum bilirubin of which the conjugated fraction does not exceed 15%. This is most often related to abnormalities in the turnover of red blood cells. A list of considerations in the differential diagnosis is listed below.

I. Hemolysis

- A. Extravascular hemolysis of red blood cells (positive indirect immunoglogulin)
- B. Arterio/veno bypass circuits
- C. Congenital or acquired defects listed below

    1. G6PD deficiency
    2. autoimmune hemolytic anemia
    3. drug induced hemolytic anemia
    4. Paroxysmal cold/nocturnal hematuria (as rare as chicken's teeth)

II. Hematoma resorption

III. Gilbert's/Crigler Najjar Syndrome

Gilbert's syndrome is a hereditary nonhemolytic intermittent jaundice associated with increases in unconjugated bilirubin. There is impaired hepatic clearance but otherwise normal hepatocellular function. It occurs in 3-7% of the population and is 2-7 times more common in males. A deficiency of hepatic UDP glucuronyl transferase has been identified as the defect. Decreased caloric intake, intercurrent illness and vomiting can cause jaundice.

Crigler Najjar, types I and II are the extreme expressions of Gilbert's syndrome and associated with minimal levels to complete absence of UDP glucuronyl transferase. These syndromes are usually detected early and are often associated with severe neurological damage due to kernicterus.

### Diagnostic Tests

The following tests should be sent to aid diagnosis:

1. CBC and smear
2. Indirect immunoglobin (indirect Coomb's)
3. ANA, and RF

### Conjugated Bilirubin

Any elevation in the conjugated bilirubin fraction always signifies hepatobiliary dysfunction. This is found in both biliary and hepatocellular disease and therefore does not help to distinguish between the two disorders. More commonly, a mixed picture of conjugated and unconjugated hyperbilirubinemia exists with most hepatobiliary disorders.

Elevation of the alanine transaminase with or without aspartate transaminase usually indicates hepatocellular inflammation or necrosis. In contrast, increases in alkaline phosphatase, gamma glutamyl transferase or 5'nucleotidase incriminate cholestasis or obstructive jaundice.

Inn and extrahepatic biliary obstruction (obstructive jaundice) present with similar clinical and laboratory findings and are usually identified on the basis of ultrasound imaging. A differential diagnosis is listed below.

I. Obstructive Jaundice (Conjugated hyperbilirubinemia)

A. Extrahepatic Obstruction

1. Tumor: biliary, pancreas and duodenal
2. Calculous and acalculous cholecystitis
3. Pancreatitis
4. Biliary stricture
5. Sclerosing cholangitis
6. Ascending cholangitis

B. Intrahepatic Obstruction

This is almost a diagnosis of exclusion or one that is established by liver biopsy. A list is given below.

1. Primary biliary cirrhosis
2. Drugs
3. TPN
4. Steroids
5. Liver transplant rejection

II. Hepatocellular Disease

Hepatocellular disease is the other category that may give rise to unconjugated or mixed hyperbilirubinemia. The differential diagnosis is extensive and includes the following problems.

A. Infectious hepatitis (Hepatitis A, B, C, D, and E, CMV, Epstein Barr virus and others)
B. Drugs/-Toxins; There are over 600 drugs listed that cause hepatic injury. Generally two categories exist; idiosyncratic reactions and dose-dependent reactions.
C. Sepsis
D. TPN (abnormal LFTs in 68-93% of individuals given > 2weeks therapy)
E. Metabolic (low PaC02/PaO2)
F. Ischemia. This is a complex topic but generally a fall in perfusion pressure due to increased venous or decreased arterial pressure will result in suboptimal oxygen delivery. Contributing factors are given in the following list.

1. Increased Venous Pressure

a. Increased infra-abdominal pressure
b. IPPV/PEEP
c. Congestive heart failure
d. Pulmonary hypertension
e. Pulmonary embolus
f. Surgical manipulation

2. Decreased Arterial Pressure

   a. Prolonged hypovolemia. Systemic shock is not necessary to cause hepatic ischemia.
   b. Vasopressors with alpha activity
   c. Aortic crossclamp
   d. Surgical manipulation

**Halothane Hepatitis**

There are direct toxic effects of drugs that are dose related such as acetaminophen. In addition there are idiosyncratic or unpredictable reactions that are often immune based. Inhalational agents, most notably halothane has been incriminated in mild to severe cases of hepatitis. It appears that halothane is capable of causing both toxic and immune mediated reactions.

Toxic reactions are often identified by a transient elevation of the LFTs immediately following an anesthetic. This occurs in up to 30% of individuals exposed to halothane, but does not result in permanent hepatocellular impairment. In contrast immune mediated hepatitis, observed in 1/30,000 exposures, causes significant morbility and mortality.

Halothane is metabolized by the liver and produces reactive acyl chloride, which acts Immunologically as a hapten. This results in trifluoroacetylation of hepatocyte membranes. The membrane-hapten complex induces an immune response resulting in hepatocyte necrosis.

Risk factors associated with halothane hepatitis include obesity, female gender, familial factors and prior exposure. The response is delayed and usually observed 7 to 28 days following exposure. Signs and symptoms of autoimmune dysfunction are observed and include:

1. pyrexia
2. arthralgia
3. rash
4. eosinophilia
5. autoantibodies
6. circulating immune complexes

Diagnostic tests must include a full panel LFT, CBC and differential and autoimmune panel. If halothane hepatitis is strongly suspected, there are several centers in the USA and Europe that test for immune-modified hepatocyte complexes.

Enflurane has also been associated with immune based hepatitis and has an incidence of 1/800,000. There also have been a few case reports of isoflurane hepatitis. In general, the potential of an inhalational agent to induce immune complexes may be partially related to the extent of metabolism as shown.

Halothane > Sevoflurane > Enflurane > Isoflurane > Desflurane

## POSTOPERATIVE RESPIRATORY FUNCTION

The introduction of general anesthetic agents facilitated intra-abdominal exploration in surgical practice. As these procedures became more common, however, the incidence of postoperative pulmonary complications also increased (1). Early observations suggested that generalized reduction in lung volumes may cause pulmonary dysfunction observed following surgery (2). Subsequently, in 1932 functional residual capacity (FRC) was identified as one of the most important lung volumes to predict outcome (3). Since that time, there has been a growing interest in the effects of intra-abdominal surgery on lung function.

One of the primary interests in pulmonary function has been the prediction of outcome following surgery. In this respect, pre-operative pulmonary function tests have been tested and used extensively. Post-operative pulmonary function tests are, also studies of outcome and may be used as predictors of potential complications. In this way, they may aid in therapeutic intervention.

Studies of post-operative lung function have been mainly descriptive and concentrated on changes in pulmonary mechanics. In spite of these detailed studies, very little is known about control of respiration and changes in ventilatory patterns. The following will provide an outline of current information regarding descriptive pulmonary mechanics.

### Pulmonary Mechanics

Studies of pulmonary mechanics have used clinical outcome to measure of predictive potential. The data is derived from both prospective clinical studies and laboratory investigations. Experiments have shown that while there is a decrease in total lung capacity post-operatively, the major volume loss occurs in FRC and vital capacity (VC) (4,5,6). The importance of these latter changes lies in their ability to identify possible respiratory morbidity.

The changes in VC following intra-abdominal surgery are larger than those in FRC, but do not correlate well with pulmonary complications (4,5,6). Instead, the best correlation is between FRC, hypoxemia and pulmonary complications (6,7). Following intra-abdominal surgery, VC is decreased by 60 percent of the pre-operative value and remains depressed for at least 5 to 7 days (4,5). In contrast, a 30 percent fall in FRC does not occur until 16 hours following surgery and returns to within normal limits by day 7 (4,5). The degree of hypoxemia is closely associated with losses in FRC. Both demonstrate a similar time delay in onset and larger reductions in FRC are also associated with greater falls in arterial oxygenation (4). This is not as obvious with changes in VC. Finally, several studies have shown a predictable relationship between degree of hypoxemia and incidence of pulmonary complications (4-6).

Therefore, it appears that measurements of FRC may provide the best insight into respiratory outcome, although the precise specificity and sensitivity are unknown. The role of VC in determining outcome is not as clear as FRC. There is, however, a weaker but apparent relationship between the magnitude of change in VC and ventilatory impairment in some studies (8).

### Site of Surgery

Not all types of surgical procedures produce comparable changes in lung volumes post-operatively (4). In terms of volume changes, the site of surgery appears to influence the degree of ventilatory change. Upper abdominal surgery demonstrates the largest impact on post-operative lung volumes and requires the longest recovery times (3,4). This is followed by lower abdominal and then posterior surgery (4). Superficial and peripheral surgery under general anesthesia is not associated with significant or ongoing respiratory problems (4). The use of regional anesthesia for superficial surgery does not result in any changes of lung volumes from pre-operative values (4).

Within the category of upper abdominal surgery, there are differences in pulmonary outcome based upon type of incision and surgical approach. Following open cholecystectomy, greater changes in lung capacities and arterial oxygenation are identified after midline rather than subcostal incisions (8). For other types of upper abdominal procedures, both midline and paramedian surgical approaches have the greatest respiratory impact (9). Esophagectomy patients have greater changes following thoracolaparotomy than a two incision laparotomy and thoracotomy (10). Laparoscopic upper abdominal surgery is associated with significantly smaller changes in pulmonary mechanics than open approaches (11).

From the preceding information it is apparent that both site of surgery and type of incision can be important determinants of respiratory outcome. The underlying reasons for these differences are unclear; however, alterations in central respiratory control have been suggested (12). Ventilatory rate and pattern, which are representative functions of central control, are altered postoperatively. The type and degree of abnormality is most apparent following midline incision for upper abdominal surgery (8). These changes may represent one of the final links to understanding respiratory dysfunction.

**Mechanism of Hypoxemia**

Prolonged post-operative hypoxemia is an early clinical manifestation of the respiratory changes, which result in pulmonary complications. The principal causes of late and prolonged desaturation have been examined in several studies (13-15). In particular, the relative contribution of altered ventilation/perfusion ratios and shunt fraction have been investigated. Results indicate that venous admixture secondary to increased shunt fraction is the main cause of hypoxemia following upper abdominal surgery (14-1 5).

The cause of increased shunt fraction is due to changes in the relationship between closing volume (CV) and FRC (6,15). Closing volume, the lung volume at which small airway begin to obstruct, contains the majority of shunt fraction. Venous admixture results from gas trapping and atelectasis secondary to collapse of small airways (15). Although, CV remains relatively constant following surgery, FRC has been shown to drop significantly post-operatively (6,16). Closing volume, then occupies a larger proportion of the total lung capacity and tidal ventilation occurs within or just above CV. The result is little or no reserve remaining during respiration.

**Alterations in FRC**

To date, the reasons for the fall in lung volumes and particularly FRC following upper abdominal surgery are not fully understood. A number of potential contributing factors have been studied and their roles clarified. The following is a review of these considerations:

**General Anesthesia**

Initially many investigators felt that continued the pulmonary effects of general anesthesia into the post-operative period may have accounted for some of the prolonged respiratory defects identified. Indeed, similar changes in FRC were identified following induction of general anesthesia (17). These mechanical alterations also correlated with a fall in arterial oxygenation (18). However, ventilation/perfusion mismatch plays a larger role in producing hypoxemia during anesthesia than post-operatively. Furthermore, recovery of FRC and hypoxemia have been observed in the early post-operative period before the subsequent fall that is associated with prolonged desaturation and pulmonary complications following upper abdominal surgery (11, 18). This alone strongly suggests a different cause.

**Pain**

Post-operative pain has also been cited as a factor that may alter pulmonary mechanics. Clinical studies have compared various forms of analgesia to determine the impact upon the respiratory system.

A series of investigators used epidural block in cross over studies to provide analgesia to the thoracic dermatome four level with minimal motor impairment (19-20). It had been demonstrated that epidural by itself at that level did not affect pulmonary function. Following surgery, epidural local anesthetics provided good analgesia but failed to correct FRC. There was a significant improvement in VC. Overall there appeared to be less pulmonary complications in the epidural as compared to narcotic group (20). This has been attributed to the improved ability to cough and clear secretions, based upon greater VC. However, even with good control of pain, post-operative respiratory, complications still occurred. The effect of improved VC on outcome demonstrated the complexity of this situation.

Unilateral intercostal blockade demonstrated small but significant improvements in VC (21). This was also accompanied by slight improvements in patient outcome. Bilateral intercostal blockade, however, had an adverse effect on both pulmonary function and patient outcome. Transcutaneous nerve stimulation (TENS) has been reported to provide sparing effects on both FRC and VC (22). Further studies are needed to confirm these beneficial effects.

**Position and Age**

It has been shown that pulmonary gas exchange is affected by posture in specific age groups (16). Post-operatively, patients are usually placed supine. This position has been shown to increase the severity of hypoxemia by a reduction in lung volume. This results from pressure on the diaphragm by the intra-abdominal contents. There is a decrease in all lung volumes except residual volume (18). The expiratory reserve volume is significantly decreased. Closing volume does not change significantly with position, but FRC decreased. This increased the chance of breathing within CV, resulting in underventilated and over perfused regions.

Age by itself is an independent variable determining the relationship between FRC and CV (17). As age increases, FRC remains constant, but CV increases. It has been found that once breathing occurs within CV, that the supine position will worsen gas exchange due to the mechanisms outlined above. In general, by age 44, breathing occurs within CV in the supine position. This was observed in the seated position by age 65.

**Other Factors**

Other patient attributes have also been shown to affect gas exchange. These can be divided into two distinct groups: those that decrease FRC and those that increase CV. Within the first group, obesity and pregnancy are significant factors (12). Smoking and pulmonary edema contribute to the second group. Pulmonary disease represents a combination of the above features, depending on the nature of the disease. Pneumoperitoneum has also been suggested to affect respiratory outcome by causing a fall in FRC (4,6).

## REFERENCES


1. Pasteur W. Active lobar collapse of the lung after abdominal operations: a contribution to the study of postoperative lung complications. Lancet 1910, 2, 1080-1083

2. Haldane J.S., Meakins J.L., Priestley J.G. The effect of shallow breathing. J. Physiol., 1919, 52, 433-453.

3. Beecher H.K. Effect of laparotomy on lung volume; demonstration of a new type of collapse. J. Clin Invest., 1932, 12,651-658.

4. Ali J. Hechman H. Weisel R . D ., Layug A . B., Kripke B . J., B . Consequences of post-operative alterations in respiratory mechanics. Amer. J. Surg., 1974, 128, 376-382.

5. Meyers JR., Lembeck L., O'Kane A.E. Changes in functional residual capacity of the lung after operation. Arch. Surg., 1975, 110, 576-582.

6. Alexander J.I., Spemce A.A., Pankh R.K., Stuart B. The role of airway closure in postoperative hypoxemia. Br. J. Anaesth., 1973, 5, 34-40

7. Hechtman H.B., Weisel R.D., Vito L., Ali J., Berger R.L. Independence of pulmonary shunting in pulmonary edema. Surgery, 1973, 300.

8. Ali J., Khan T . A . The comparative effects of muscle transection and median upper abdominal incisions on postoperative pulmonary function. Surg. Gynecol., Obstet., 1979, 148, 836-866.

9. Knudsen J., Duration of hypoxemia after uncomplicated upper abdominal and thoraco-abdominal operations. Anesthesia, 1970, 25, 372-377.

10. Black J., Kalloor G.J., Colli- J.L. The effect of the surgical approach on respiratory function after esophagectomy. Br. J. Surg., 1977, 64, 624-627.

11. Putensen-Himmer G., Putensen C., Lammer H., Lingnauw., Algner F. Benzer H. Comparison of postoperative respiratory, function after laparoscopy or open laparoscopy for cholecystectomy. Anesthesiology, 1992, 77. 675-680.

1. Craig D.B. Postoperative recovery of pulmonary function. Anesthesia and Analgesia, 1981, 60. 46-52.

13. Vaughan R. W., Wise L. Postoperative arterial blood gas measurement in obese patients: effect of position on gas exchange. Ann. Surg.,1975, 183, 705-709.

14. Colgan F.J., Mahoney P. The effects of major surgery on cardiac output and shunting. Anesthesiology, 1969, 31, 213-221.

15. Siler J.N., Rosenberg H., Mull T.D., Kaplan J.A. Hypoxemia after upper abdominal surgery: comparison of venous admixture and ventilation /perfusion inequality components, using a digital computer. Ann . Surg ., 1974, 179, 149-155.

16. Craig D.B., Wahba W.M., Don H. F., Couture J.G., Becklake M.R. "Closing volume" and its relationship to gas exchange is seated and supine positions. J. Appl. Physiol., 1971, 31, 717-721.

17. Rehder K. Anesthesia and the respiratory system. Can. Anaes. Soc. J., 1979, 26, 451-462.

I8. Marshall B . E ., Wyche M .Q . Hypoxemia during and after anesthesia. Anesthesiology, 1972, 37, 178-209.

19. Wahba W . M., Don H . F., Craig D . B . Post-operative epidural analgesia effects on lung volumes. Can. Anaes. Soc. J., 1975, 22, 519-527.

20. Spence A . A., Smith G. Postoperative analgesia and lung function: a comparison of morphine with extradural block. Br. J. Anaes., 1971, 43, 144-148.

21. Engberg G. Relief of postoperative pain with intercostal blockade compared with the use of narcotic drugs. Acta Anaesthesia Scand. (Suppl.)., 1978, 70, 36-38.

22. Ali J., Yaffe C., Serrette C., The effect of transcutaneous electrical nerve stimulation on postoperative pain and pulmonary function. Surgery, 1981.