

# **The Identification of Avoidable Risk Factors for Developing Small for Size Syndrome in Patients Undergoing Major Liver Surgery and Transplantation**

**Thesis**  
**Submitted for the partial fulfillment of**  
**M.D. Degree**  
**in**  
**General Surgery**

**By**  
**Shady Tarek M. El-Ghazaly**  
A.L. in General Surgery  
M.B.B.ch., MSc. in General Surgery

**Supervised by**

**Prof. Ezz El-Din Korashi**  
Professor of General Surgery  
Cairo University

**Prof. Salah Shaheen**  
Professor of General Surgery  
Cairo University

**Prof. Nigel Heaton**  
Professor of Transplant and Hepato-biliary Surgery  
King's College Hospital, University of London

**FACULTY OF MEDICINE**  
**CAIRO UNIVERSITY**

**2011**

*To all those God blessed me with,*

*My Beloved Wife Fatma,*

*My Lovely Sons*

*Khaled and Ali*

*And*

*My Great Parents*

# **Contents**

## **Acknowledgements**

## **List of Abbreviations**

## **List of Figures**

## **List of Tables**

## **1. Review of Literature**

### 1.1. Introduction

### 1.2. Liver Histology

### 1.3. Liver Regeneration

#### 1.3.1. Factors influencing liver regeneration

#### 1.3.2. Effect of Age on Liver Regeneration

### 1.4. Small for Size Syndrome

#### 1.4.1. Remnant liver volume

#### 1.4.2. Liver Quality

#### 1.4.3. Assessment of Hepatic function

#### 1.4.4. Portal Hypertension

### 1.5. Small for Size and Liver Transplantation

#### 1.5.1. Cadaveric Livers

#### 1.5.2. Living Donor Liver grafts

#### 1.5.3. The effect of Portal Hypertension on LT

1.5.4. The importance of Venous Outflow in Preventing SFSS	
1.6. Pathophysiology of Small For Size Syndrome	
1.7. Modulating Portal Inflow	
1.7.1. Porto-caval shunts	
1.7.2. Intraportal infusion	
1.7.3. Temporary portal vein restriction	
1.7.4. Splenic artery ligation	
1.8. Promoting growth in small for size livers	
1.9. The least recorded GRWR in a successful transplant	
<b>2. Hypothesis</b>	
<b>3. Aim of the Work</b>	
<b>4. Patients and Methods</b>	
<b>5. Results</b>	
5.1. Hepatectomy group	
5.2. Transplant group	
<b>6. Discussion</b>	
<b>7. Conclusion</b>	
<b>8. Summary</b>	
<b>References</b>	

## Acknowledgements

It is a pleasure to thank those who made this thesis possible. I owe my deepest gratitude to Professor Ezz Korashi and Professor Salah Shaheen, my supervisors, who were the best guidance I could get in the beginning of my career. I would also like to express the greatest appreciation to Professor Heaton, who continually and convincingly conveyed a spirit of adventure in regard to medical research, and has made available his support in a number of ways. Similarly, I am deeply grateful to Professor Rela, whom without his guidance and persistent help this thesis would not have been possible.

I am indebted to many of my colleagues in the Liver Institute, King's College Hospital to support me in my research. This includes my fellow surgeons, anaesthetists, transplant coordinators and nurses in the liver theatre. I would also like to thank Ragaai Metri, one of the most prominent scientists in the Liver Institute, whose help and assistance throughout my research were unlimited. In addition, a thank you to Adam Bartlett, the colleague surgeon who put me on the right tracks at the beginning of my research, and Gillian Al-Khadimi, the HCC nurse who has always been a great help for me.

I would like to thank my parents for their financial and never ending support, for the help in my study and for its success. I would also like to show my gratitude to my wife, Fatma who has been the main source of comfort and support in all difficult times. And it would not be successful without God who guides me in my everyday life and activities. I thank Him for the good health he has given to me, and for the success of my study. For all the people who helped me a lot, thank you very much and may god bless you all.

# **Abstract**

When a live transplant patient receives a small volume of graft, the postoperative liver function is not optimal. This is described as small-for-size live syndrome (SFSS), SFSS is a recognizable clinical condition after major liver surgery (transplantation & resection), characterised by postoperative liver dysfunction/failure. Overcoming this condition will allow us to transplant smaller livers into larger patients without major complications. This will encourage living donors to donate a smaller part of their liver to their sick relative with less risk to the donor, as well as a good outcome for the recipient. This study aims to understand the mechanism of the condition. This research assesses the relationship between portal pressure and the outcome of major live surgery , which might lead to the modification of surgical techniques in order to overcome SFSS.

**Key Words : Liver surgery - Transplant - Dysfunction - Failure.**

# List of Abbreviations

Alanine aminotransferase (ALT)	King's College Hospital (KCH)
Alanine aminotransferase ratio (AAR)	Kupffer cells (KC)
Alcoholic liver disease (ALD)	Leukemia Inhibitory Factor (LIF)
Apolipoprotein A (apoA)	Live donor liver transplantation (LDLT)
Asialoglycoprotein (ASGP)	Liver transplantation (LT)
Aspartate aminotransferase (AST)	Magnetic Resonance Imaging (MRI)
AST-to platelet ratio index (APRI)	Middle hepatic vein (MHV)
Blood volume (BV)	Model of End-stage Liver Disease (MELD)
Body surface area (BSA)	Modified right lobe graft (MRL)
Cardiac output (CO)	Nitric oxide (NO)
Cardiotrophin (CT)	Nitric Oxide (NO)
Central venous pressure (CVP)	Non-heart-beating donors (NHBD)
Chemotherapy associated steatohepatitis (CASH)	Nuclear factor (NF) – $\kappa$ B
Child-Turcotte-Pugh (CTP)	Orthotopic liver transplantation (OLT)
Ciliary Neurotrophic Factor (CNTF)	Paracetamol overdose (POD)
Cobalt-protoporphyrin (CoPP)	Portal hypertension (PHT)
Computed tomography (CT)	Portal venous flow (PVF)
Donation after brain death (DBD)	Portal venous pressure (PVP)
Donation after cardiac death (DCD)	Porto-systemic (PS)
Donor risk index (DRI)	Proliferating cell nuclear antigen (PCNA)
Early growth response one (Egr-1)	Prostaglandin E2 (PGE2)
Endothelin (ET)	Proximal splenic artery embolization (PSAE)
Epidermal growth factor (EGF)	Remnant liver volume (RLV)
Extended donor criteria (EDC)	Sinusoidal endothelial cells (SEC)
Galactosyl-human serum albumin (GSA)	Small for size syndrome (SFSS)
Graft-to-recipient weight ratio (GRWR)	Splenic artery embolization (SAE)
Graft volume (GV)	Splenic artery ligation (SAL)
Graft-to-recipient spleen size ratio (GRSSR)	Standard liver volume (SLV)
Heat Shock Protein (HSP)	Superior mesenteric artery (SMA)
Heme oxygenase (HO)	Superior mesenteric vein (SMV)
Hemiportocaval shunts (HPCS)	Transjugular intrahepatic portosystemic shunt (TIPSS)
Hepatic artery flow (HAF)	Tumour growth factor (TGF)
Hepatic venous pressure gradient (HVPG)	Tumour necrosis factor (TNF)
Hepatocellular carcinoma (HCC)	Tumour necrosis factor receptor (TNFR-1)
Hepatocyte growth factor (HGF)	UK End stage Liver Disease (UKELD)
Indocyanine green (ICG)	United network for organ sharing (UNOS)
Intensive therapy unit (ITU)	Vascular endothelial growth factor (VEGF)
Interleukin (IL)	

# List of Figures

- Figure 1: Orchestration of liver regeneration
- Figure 2: Decision tree for selection of operative procedure in patients with impaired liver functional reserve
- Figure 3: Flow chart showing approach to preoperative assessment for selecting patients with cirrhosis for major hepatectomy
- Figure 4: Right lobe graft implantation on the IVC
- Figure 5: A) Side –to-side mesocaval shunt with downstream ligation of the SMV.  
B) Partial PC shunt between one of the branches of the recipient portal vein and IVC.
- Figure 6: Types of hepatectomies in the hepatectomy group.
- Figure 7: Scatter plot graph showing a statistically significant correlation of INR on day 7 with HVPG (mmHg).
- Figure 8: Scatter plot graph showing the correlation of INR on day 7 with PVP (mmHg).
- Figure 9: Scatter plot graph showing a statistically significant correlation of Ascites on day 7 with HVPG (mmHg).
- Figure 10: Scatter plot graph showing a statistically significant correlation of Ascites on day 7 with HVPG (mmHg).
- Figure 11: Box plot graph showing the difference of PVP in liver grafts with none, mild and moderate fatty infiltration.
- Figure 12: Scatter plot graph showing a statistically significant correlation PVP with DRI.
- Figure 13: Box plot graph showing the difference of PVP in liver grafts with a DRI  $>1.7$  and those with DRI  $<1.7$ .
- Figure 14: Box plot graph showing the difference of PVP in NHBD grafts from heart beating grafts.
- Figure 15: Box plot graph showing the difference of PVP in patients who had ascetic drainage more than 500 ml on day 7 or afterwards and those who had not.
- Figure 16: Box plot graph showing the difference of HVPG in patients who had ascetic drainage more than 500 ml on day 7 or afterwards and those who had not.
- Figure 17: Box plot graph showing the difference of PVP in patients who spent more than 30 days in hospital and those who did not.
- Figure 18: Box plot graph showing the difference of PVP in patients who had morbidity within 30 days and those who did not.



# List of Tables

Table 1: Factors affecting the occurrence of SFSS

Table 2: Relative risk of graft failure after adjustment for confounding variables

Table 3: Adjusted 3-month, 1-year and 3-year graft survival according to donor risk index as determined by donor, graft and transplant factors (1998–2002).

Table 4: Characteristics of hepatectomy group

Table 5: Types of hepatectomy performed

Table 6: Correlations within Hepatectomy group

Table 7: Indications of transplantation in the transplant group

Table 8: Recipient characteristics

Table 9: Intraoperative pressure measurements

Table 10: Postoperative follow-up

Table 11: Correlation of PVP and HVPG with DRI

Table 12: Correlations of PVP and HVPG with Postoperative data

# **Review of Literature**

# **1.Review of Literature**

## **1.1. Introduction**

The liver has a remarkable ability to regenerate following injury or resection. The earliest allusion of the liver's regenerative capacity dates back to Greek mythology. Prometheus was punished for stealing the secret of fire from the gods of Olympus and giving it to primitive humans by being chained to a rock and having an eagle of Zeus devour his liver each day. Each night his liver regenerated leaving him fit for the following day's torture. It wasn't until the late 1800s that the regenerative capacity of the liver was documented scientifically. A variety of genes, proteins, cytokines and cells are involved in the initiation and modulation of the liver regeneration. In this review, the cells that participate in the regenerative process in the liver, factors known to influence the regenerative response and the clinical consequence of inadequate parenchymal mass and potential treatment options available, are discussed.

## **1.2. Liver Histology**

Liver parenchyma is divided into hepatic lobules by the connective tissue septa invaginating from its capsule. The lobule is a roughly hexagonal arrangement of plates of hepatocytes, which are the parenchymal cells, radiating outward from a central vein in the center, separated by blood sinusoids. Portal triads, formed from a bile duct and branches of the hepatic artery and hepatic portal vein, are regularly distributed at the vertices of the lobule. The walls of the sinusoids are lined by three different non-parenchymal cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells. Hepatocyte functions are regulated by substances released from neighboring non-parenchymal cells both under physiological and pathological conditions. Kupffer cells secrete potent mediators of the inflammatory response and thus control the early phase of liver inflammation, while stellate cells play a key role in the development of inflammatory fibrotic response following liver injury (1).

Liver regeneration is characterized by the proliferation of all existing cell lines within the liver, including hepatocytes, sinusoidal endothelial cells, Kupffer and stellate cells. Hepatocytes swell due to an increase in intracellular triglyceride, leading to mild hepatic steatosis (2-4). DNA synthesis begins within the first 24 hours after resection and is characterized by an increase in mitotic rate and density of chromatin. Cellular proliferation starts in the periportal areas of the liver and spreads to the pericentral area, resulting initially in the formation of disorganized

clumps of cells, which undergo remodeling after the deposition of collagen types I and IV (2;5).

Histologic features of small for size syndrome include cholestasis with bile plugs, and areas of regeneration and ischaemia with patchy necrosis (6;7). The mechanism by which this occurs following parenchymal resection, is thought to be due to a reduction in the intra-hepatic vascular bed leading to higher portal flow per gram of remnant liver (8;9). It is postulated that the increased hepatic portal pressure leads to transient sinusoidal narrowing, endothelial injury, Kupffer cell activation and release of pro-inflammatory cytokines, and consequently an impairment of liver regeneration (10;11).

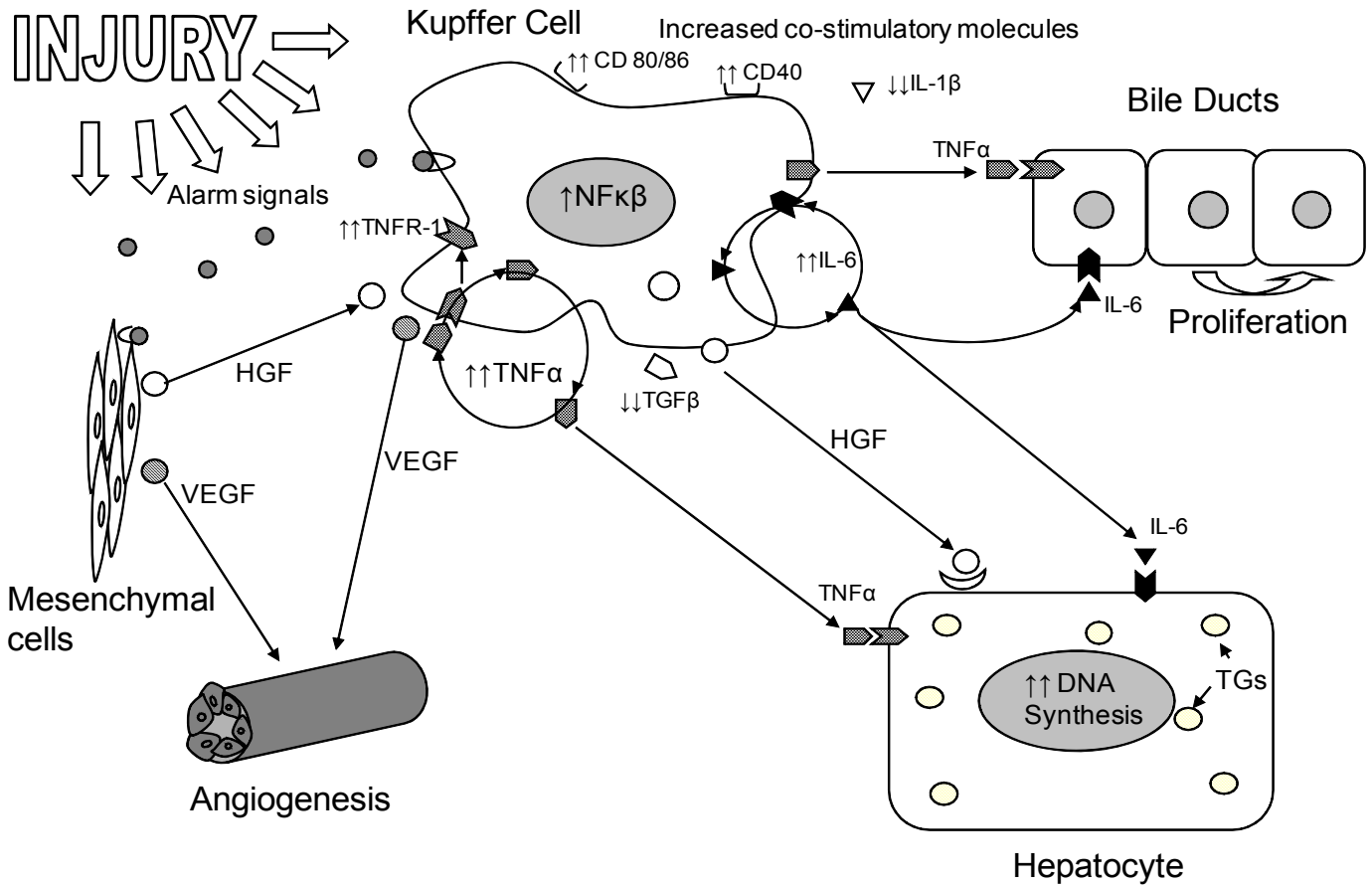
### 1.3. Liver Regeneration

Liver regeneration after partial hepatectomy is a perfectly calibrated response whose apparent sensor is the body's requirement for liver function (12). The liver regenerates following injury, ischaemia or resection, but resection is the strongest stimulator of hepatic regeneration (13). Regeneration starts approximately 72 hours following tissue loss and is usually complete within 3–6 months (14). Following liver resection, re-growth of the liver remnant occurs by compensatory hypertrophy rather than true regeneration. The regenerative response is proportional to the degree of tissue loss up to 70% of the parenchymal mass, then there is a decline in the intensity of the response (15).

The orchestration of this complex physiological response is dependent on numerous cytokines, growth factors, and metabolic networks (16) [Figure 1]. Liver resection reduces the liver mass, but leaves few injured cells. 'Alarm signals' released by the injured cells are thought to trigger hepatic regeneration and have been the subject of intense investigation, but remain elusive. The liver specific tissue macrophages, Kupffer cells, play a central role in mediating the process. Following liver injury, the Kupffer cells are activated through the binding of tumour necrosis factor (TNF)  $\alpha$  to tumour necrosis factor receptor (TNFR-1), leading to activation of nuclear factor (NF)  $\kappa$ B, and the release of proinflammatory cytokines, including interleukin (IL) -6, and TNF-  $\alpha$ . IL-6 is a family of proteins that includes oncostatin M, Leukemia Inhibitory Factor (LIF),

Ciliary Neurotrophic Factor (CNTF), Interleukin 11 (IL-11) and cardiotrophin (CT) (17).

**Figure 1: Orchestration of liver regeneration**



● Non-foreign alarm signals are released from cells injured during hepatectomy and include: mammalian DNA, RNA, heat shock proteins (Hsps), interferon- $\alpha$ , interleukin-1b, CD40-L (a surface molecule on activated platelets and activated T cells), and breakdown products of hyaluron (made when vessels are damaged)(18)

○ HGF released from mesenchymal cells as well as Kupffer cells after their activation

● VEGF released from mesenchymal cells as well as Kupffer cells after their activation

▽ TGF- $\beta$ , which is an antiproliferative cytokine produced by Kupffer cells, is inhibited [Non-parenchymal cells]

△ IL-1 $\beta$ , which is an antiproliferative cytokine produced by Kupffer cells, is inhibited [Non-parenchymal cells]