AN INVESTIGATION OF LIVER BLOOD FLOW IN SYSTEMIC INFLAMMATION

by

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DEDICATION

To my children Jamie and Holly, without whom this would have been finished a good deal quicker.

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DECLARATION

I declare that the work presented in this thesis has been carried out solely by myself except where indicated below.

I started this work in 2002 while working as a research fellow in the University Department of Surgery, Glasgow Royal Infirmary. I continued this work following my appointment to Specialist Registrar posts in the West of Scotland.

The intra-observer measurements of liver blood flow in the control group were carried out with the assistance of Dr John McQuarrie.

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Statistical analysis was carried out with the assistance of Drs Wilson Angerson and Donald McMillan.

PRESENTATIONS

- Evaluation of liver haemodynamics in intensive care patients with Systemic Inflammatory Response Syndrome. Radiological Society of North America, Chicago, 1st-6th December 2002. Oral presentation.
- The systemic inflammatory response and liver blood flow in critically-ill patients. European Society of Enteral and Parenteral Nutrition, Cannes,

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- The systemic inflammatory response and liver blood flow. Scottish Intensive Care Society, Stirling, 23-24th January 2003. Oral presentation
- Liver blood flow changes in critically ill patients. British Association of Parenteral and Enteral Nutrition, Telford, November 2003. Poster presentation.
- Liver haemodynamic response to systemic inflammation. West of Scotland Intensive Care Society, Victoria Infirmary, Glasgow, 11th February 2003. Oral presentation. Won meeting prize.

ABSTRACTS

- Evaluation of liver haemodynamics in intensive care patients with Systemic Inflammatory Response Syndrome (SIRS): preliminary results. P Glen, D McMillan, J Kinsella, W Angerson, E Leen. *Radiology* (supplement.) Nov 2002. 225(p), pp485-6
- The systemic inflammatory response and liver blood flow in critically-ill patients. P Glen, DC McMillan, E Leen, J Kinsella. *Clinical Nutrition.* August 2003. 22 (S1), p(s)53
- The systemic inflammatory response and liver blood flow in critically-ill patients. *P Glen, DC McMillan, E Leen, J Kinsella. Proceedings of the Nutrition Society* 2003.

PUBLICATIONS

- The relationship between hepatic arterial and portal venous blood flows following elective arthroplasty. Paul Glen, Wilson J Angerson, John Kinsella, Donald C McMillan. Submitted to press.
- A study of hepatic arterial and portal venous blood flow in the critically ill patient. Paul Glen, Donald C McMillan, Wilson J Angerson, John Kinsella. Submitted to press.

OVERVIEW

The research interests of the department in which this study was performed include systemic inflammation as a prognostic factor in malignant disease and the role of liver blood flow as a prognostic indicator in cancer. We initially wished to link the liver blood flow changes seen in advanced cancer to indicators of systemic inflammation in the most inflammed patients in the hospital, the intensive care patients. Alongside scanning the intensive care patients, studies were performed in control, malignant and hepatitic patients to corroborate findings of previously published results. Studies in intensive care patients were not able to assess changes in blood flow at the onset of illness and a surgical traumatic insult was used as a controlled inflammatory stimuli.

This study was a novel pilot study and it was not possible to perform any power calculations, instead similar historical studies were used as a guide as to what number of patients would be likely to give meaningful results.

SUMMARY

Inflammatory stimuli such as infection or tissue injury will produce a local inflammatory response which may, if the inflammatory response is sufficiently large, spill over to produce a systemic inflammatory response. This is clinically characterized by a response in heart and respiratory rate, a temperature rise or fall and a white cell response. Where the systemic inflammatory response syndrome is due to proven infection this is classified as sepsis. If the inflammatory stimulus is removed or dealt with by the body or with medical treatment, the systemic inflammatory response may resolve with a return to homeostasis. In some patients the response does not resolve and they may progress to an anti-inflammatory state which predisposes to infection and poor wound healing or progress to multi-organ dysfunction syndrome, often resulting in cardiac, respiratory or renal failure. There is no specific treatment for multi-organ dysfunction syndrome and the practice of intensive care medicine has developed to support organ function in this period while the source of the illness is treated and the patient allowed time to recover. Mortality remains high in intensive care medicine with in hospital mortality around 30-40%.

Clinically markers of systemic inflammation are used to assess improvement or deterioration in condition. White cell count will be elevated in infection and is not a good indicator of systemic inflammation. The pro-inflammatory cytokines such as IL-6 mediate inflammation. These are secreted by activated macrophages of which 80% are resident in the liver as Kupffer cells. Cytokines act on the liver hepatocytes causing them to produce proteins. Plasma proteins that change in concentration with inflammation are named acute-phase proteins and the most clinically important of

these is C-Reactive Protein. It is usually found in the plasma at concentrations of 3mg/l or less and values of less than 10mg/l are regarded as clinically unimportant. C-reactive protein is stable in plasma, does not increase with age, has little or no diurnal variation, changes rapidly with disease and has a wide range of abnormal values.

The liver is a source of cytokines, a target for cytokines, manufactures proteins and is the site of gluconeogenesis in systemic inflammation and thus plays a pivotal role in the process. In humans liver failure is rare in multi-organ dysfunction syndrome; however liver dysfunction is associated with poorer outcome in critical illness. As the liver is hypermetabolic the delivery of blood would appear to be important in critical illness.

Liver blood flow has been studied in systemic inflammation but the relative inaccessibility of the portal vein and the hepatic artery has made this a difficult task. The few studies that have been performed in critically ill patients have used the Fick principal to allow estimation of total liver blood flow by clearance of a marker in the blood by the liver. A requirement of this technique is hepatic venous catheterisation which is invasive and not without complications. Advances in ultrasound technology have allowed colour Doppler/ duplex scanning of the hepatic artery and portal vein trans-abdominally and allow non-invasive measurement of not only total liver blood flow but also its individual components. This technique has been shown to be reliable and reproducible and the results reported in Chapter 2 confirm with this in the authors' hands.

The consensus from previous work is that total liver blood flow is increased in systemic inflammation. As mentioned above the relative contributions of the hepatic artery and portal vein in these changes has not been studied. In Chapter 3 a cross sectional study was performed in three different groups; controls, non-small cell lung cancers and acute alcoholic hepatitis. These three groups were shown to be different in levels of systemic inflammation with the controls least and the hepatitics most inflamed. Total liver blood flow was not significantly altered in these inflammatory disease states, nor was portal venous blood flow. In contrast, there was a significant increase in hepatic arterial blood flow which was related to increased systemic inflammation. The mediators of the increased hepatic arterial flow was not clear but it could be a hormonally mediated response, a cytokine mediated response or simply an intrinsic response to the increased metabolic demand that on the liver by systemic inflammation.

Previous liver blood flow studies in acute inflammation have been performed when inflammation is established and therefore it is difficult to define the chronological changes in liver blood flow. A previous study utilised ultrasound to measure the liver blood flow at 5 and 24 hours after onset of inflammation. This study reported an increase in hepatic arterial and portal venous blood flow at 5 hours compared to controls but no significant changes at 24 hours. Studies with infusions of interleukin-6 demonstrated an increase in liver blood flow that peaked at four hours in healthy volunteers. We therefore hypothesised that there were changes in hepatic arterial and portal venous blood flow within the first 6 hours of an inflammatory stimulus. In Chapter 4 serial hepatic arterial and portal venous blood flow measurements were made following the surgical trauma of lower limb arthroplasty. An immediate fall in

portal venous flow was seen which was followed by an increase in hepatic arterial blood flow over the next four hours. By 24 hours the hepatic arterial blood flow was not significantly different to the pre-operative value and the portal venous flow was returning to normal, although remained statistically lower than pre-operatively.

The immediate fall in portal venous flow is likely to be hormonally mediated, as we know the adrenal medullary hormones that are released in response to tissue injury or trauma, will direct blood away from the gut to selectively perfuse the brain, heart, lungs, kidneys and muscle. The immediate effect would also favour a hormonal rather than a cytokine response. The liver will immediately have a metabolic stress placed on it as it as gluconeogenesis is stimulated in hepatocytes. After a period of time following tissue injury the Kupffer cells of the liver will begin to transcript for cytokines and the liver hepatocytes will be stimulated by these cytokines to manufacture acute phase proteins. Whether the late increase in hepatic arterial flow is a direct effect from cytokines or a reactive response to increased metabolic rate in the liver is not readily addressed by this study.

Finally, we wished to assess changes in blood flow in the intensive care setting. It has previously been reported that total liver blood flow is increased in critical illness compared to controls. Studies over time have suggested that initially there is an increase in total liver blood flow compared to controls; however no significant change after 24 hours. In Chapter 5 hepatic arterial and portal venous blood flows were measured in intensive care patients during their ITU admission. There was no correlation between blood flows and level of systemic inflammatory response as assessed by C-reactive protein. A greater variability in blood flow measurements was

seen in non-survivors. The absence of drop in portal flow may be explained by aggressive fluid resuscitation in the first 24 hours of the ITU stay. The absence of an increase in hepatic or total liver blood flow was not clear.

The present thesis identified changes in hepatic arterial and portal venous blood flow between groups of patients and following an inflammatory stimulus. Future work requires to examine which hormones and cytokines modify liver blood flow. This may be assessed by repeating the study in Chapter 4, where liver blood flow was measured following surgery, and by sampling blood for hormonal and cytokine analysis. If the intrinsic control of the liver is responsible for these changes it would be important to show that the liver is more metabolic as the changes occur. An intervention to lower the metabolic demand on the liver is difficult and may not be ethical given that the normal response to injury or infection is an acute phase response. One area where this could be said to have been performed is the tight control of blood glucose in intensive care medicine which reduces the demand on the liver to perform gluconeogenesis. While there are other benefits of lower serum glucose levels this may contribute to the reported improved outcome in such patients.

Clinically, measurement of hepatic arterial and portal venous blood flow has been shown to be feasible in the critically ill patient and may be used as a non-invasive measurement of the liver response to a drug or therapy.

Chapter 1: Introduction

1.1 **Response to injury**

The four classical signs of local inflammation are rubor (redness), calor (heat), dolor (pain) and turgor (swelling). These signs appear whether one has a cut to the skin, a burn to skin or boil under the skin and can be readily understood as a local response which increases the blood supply to the affected area and increases capillary permeability thus delivering the appropriate blood cells to fight infection or building blocks to repair tissue, while providing an environment hostile to bacteria and moist to prevent drying out of damaged tissues.

This local response also produces proteins that act as signals to other cells locally. These proteins have been classed as cytokines/ chemokines and act on blood vessels to increase their diameter and permeability to plasma proteins. If this cytokine/ chemokine response is sufficiently large it stimulates a systemic response in other organs distal to the injury which has been termed the acute phase response or more correctly the systemic inflammatory response (1).

Even in the 18th century the concept of a total body response to local injury was beginning to be recognised. The earliest observation of this was by John Hunter(2) in 1794 who stated in his publication, "Treaties on the blood, inflammation and gunshot wounds" that "There is a circumstance attending accidental injury which does not belong to disease, namely, that the injury done, has a tendency to produce both the disposition and the cure." In 1852 Cole (3) made the observation, "The arteries contract and retract to the saving of many a life…. Whether haemorrhage will or will not follow a gunshot wound mainly depends on the amount of physical prostration

and collapse produced by the violent shock to the system." Malcolm (4) described a systemic response to injury in 1893, telling us "shock is more a part of the phenomena caused by injury, surgical or otherwise, than a complication thereof." He termed the systemic response of pyrexia 'Traumatic Fever'.

Cuthbertson developed this concept of a systemic multi-organ response rather than only a local tissue response to injury. He describes two phases of response. Initially a short 'ebb phase' or 'wound shock,' lasting a few hours, during which there is relative or absolute anuria, decreased heat production and body temperature and decreased nitrogen excretion. A flow phase, lasting a few days was then described during which there is a marked urinary loss of nitrogen, sulphur and phosphorous, increased heat production and increased body temperature. The urinary losses were such that they could not be part of a local tissue response alone and he concluded that the healing process required breakdown of protein mass from other tissues in particular skeletal muscle (5).

Subsequently, this flow phase response injury was found to result in increased plasma levels of amino acids, derived from skeletal muscle tissue; and increased liver gluconeogenesis from amino acids (6). The consequent hyperglycaemia was found to be resistant to the supplementation of insulin (7) and there were increased plasma concentrations of the counter regulatory hormones; cortisol, glucagon, and adrenaline. Indeed, when these three hormones were infused separately there were transient increases in hepatic glucose production. Furthermore when they were infused together this lead to a prolonged elevation of glucose production and a synergistic response was evident (8).

It is also of interest that there were increases in cardiac output and changes in organ blood flow both following significant injury (9) and after glucagons (10) or adrenaline (11) infusion. Levels of the triple hormones equivalent to the infusion studies were found to be associated with increases in blood flow. In particular there was an increase in splanchnic blood flow whereas renal blood flow was unaltered (9). One explanation is that the liver being central to substrate metabolism requires increased delivery of oxygen, nutrients and substrates and thus requires increased blood flow. These workers were not able to distinguish the blood flow to the liver from the other components of splanchnic blood flow. Animal studies have not appeared to be useful in this regard since, following an inflammatory stimulus, there appears to be a decrease in blood flow inconsistent with human studies (12-14).

The effect of the triple hormone infusion on acute phase protein production and nitrogen balance was not as profound as that seen in equivalent injury (15;16). This indicated that some other messenger or messengers was involved in the systemic inflammatory process (16). In the last decade or so there has been a great deal of interest in the role of cytokines/ chemokines/ leukotrienes in the systemic inflammatory response. This originates from work on a heat labile protein from activated leukocytes that caused a systemic fever when injected peripherally (17). This substance was variously termed granulocytic, leukocytic or endogenous pyrogen (EP). Until 1974 it was assumed that EP was a single molecule, however Dinarello and co-workers (18) characterized two distinct molecules derived from human monocytes and for the remainder of this decade a number of molecules with similar properties and different chemical characteristics were being identified (19). It became

apparent that EP was the same molecule as lymphocyte-activating factor which was subsequently termed as interleukin-1. IL-1 had previously been studied as leukocyte endogenous mediator and was found to increase synthesis of acute phase liver proteins and liver RNA (20). As well as fever and acute phase protein induction, IL-1 appeared to cause the release of amino acids from muscle in vitro (21;22), as similarly seen in patients with elevated cortisol, glucagon and adrenaline levels.

IL-1 was the first molecule to be endogenously purified and characterized as both a pyrogenic and lymphocyte-activating molecule; however two other molecules shared these characteristics and could also induce acute phase protein production. These were interleukin-6 (IL-6) and tumor necrosis factor (TNF). TNF is a macrophage product so named as it has a direct cytotoxic effect on certain tumour cells. It shares many biological properties with IL-1, however their amino acid sequences differ significantly (23). Consistent with this framework, following the stress hormonal response, TNF is the first cytokine to be found in elevated concentrations in the plasma, around two hours following injury (24) as it is continually transcribed by macrophages (25). IL-1 is the next cytokine that appears and this is followed by IL-6. IL-6 appears later as its gene expression must be induced. This expression is enhanced by the presence of IL-1 but especially by IL-1 plus TNF (26).

Release of these pro-inflammatory cytokines also stimulates release of anti-inflammatory cytokines (e.g. IL-4 and IL-10) and cytokine soluble receptors to bind to the pro-inflammatory cytokines. As combinations of cytokines act on target cells and may as a result have an additive, inhibitory or synergistic effect (27).

Systemic inflammation occurs where there is a loss of control of the local inflammatory response and there is a systemic spill over of pro-inflammatory cytokines (28). This response is thought to enhance the recruitment of blood products to the site of inflammatory stimulus. If the stimulus is then blocked or resolved, anti-inflammatory cytokines, hormones and other factors return the body to homeostasis. If the inflammatory stimulus continues we see loss of regulation of the inflammatory response and a systemic inflammatory response syndrome. Several genetic factors which make the progression of systemic inflammation to multiple organ dysfunction syndrome more likely, have been identified and certain individuals may be predisposed to increased severity of illness (29;30) as their expression of pro- and anti- inflammatory agents is altered.

Clinically, causes of a systemic inflammatory response syndrome that we see in the intensive care setting include infection, trauma (including surgery), burns, tissue infarction and pancreatitis. The development of this response can be thought of as a 'kill or cure', allowing the body to fight infection/ heal itself or die trying. With developments in intensive care medicine over the last 50 years, we can support a number of organs while treating the stimulus to the inflammation. Therefore, a continuing systemic inflammatory response may well be detrimental to the outcome overall.

1.2 **Aetiology, clinical course and treatment of the systemic inflammatory response in the critically-ill patient**

The systemic inflammatory response syndrome describes a spectrum of stereotypical changes in host metabolism which vary in magnitude and duration. This ranges from individuals who resolve their inflammatory response without intervention to cases in which modest intervention such as antibiotics or elective surgical intervention will be required and to those patients who will require specialist care in a critical care setting.

Those patients with significant disturbance of their body homeostasis require definition of pathologies and grading of the different levels of response to the injury or insult. Definitions of critical illness and scoring systems to describe severity of illness have been developed to attempt to overcome this problem.

Until 1992 there were many terms being used without clear definitions for the same phenomenon that was seen in these patients. The presence of an inflammatory stimulus, the physiological response of tachycardia, tachypnoea, pyrexia and white blood cell response, the progression onto hypotension and the further progression into multi-organ failure were variously named sepsis, severe sepsis, shock, multi-organ failure or systemic inflammation. These terms were not specific and therefore potentially confusing. In 1991 the members of the American College of Chest Physicians and the Society of Critical Care Medicine held a consensus conference (31) and decided on the following standardised definitions.

- Systemic Inflammatory Response Syndrome (SIRS)

A response to an inflammatory stimuli resulting in two or more of the following clinical manifestations:

a) a body temperature of >38°C or <36°C
b) a heart rate of >90 bpm
c) tachypnoea, a respiratory rate of >20 or hyperventilation, $PaCO_2$ <4.3kPa
d) an alteration of WCC of >12,000 cells/mm^3, or <4000cells/mm^3, or the presence of >10% immature neutrophils.

- Sepsis

The presence of Systemic Inflammatory Response Syndrome as the result of a proven infectious process.

- Severe Sepsis

Sepsis associated with organ dysfunction, hypoperfusion or hypotension (systolic blood pressure <90mmHg or reduction of 40mmHg or more, from baseline). Hypoperfusion and perfusion abnormalities may include lactic acidosis, oliguria or an acute alteration in mental status.

- Septic Shock

Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Blood pressure may be normal in the presence of inotropic support but a patient is still considered to have septic shock if hypoperfusion abnormalities are present at this time.

- Multiple Organ Dysfunction Syndrome

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

These definitions have enabled studies looking at prognostic values and therapeutic interventions in intensive care patients to be standardised. Ten years after these definitions were introduced, a further consensus group of physicians working in critical care met to discuss if they could improve upon the original definitions (32). Their findings were that the 1992 guidelines required no modification other than to expand the list of signs and symptoms of sepsis.

1.2.1 Assessment of magnitude of inflammatory response by use of a severity score

Critical illness develops in a wide range of specialties and in this heterogeneous group it has always been difficult to compare outcomes and clinical management. A scoring system of illness severity is required for audit and comparison of intensive care units, which can also be used to predict outcome. For this purpose the APACHE II (acute physiological and chronic health evaluation) scoring system (33) is most commonly used. APACHE II derives an acute physiological score in the first 24 hours of admission from 12 basic physiological indices including temperature, cardiovascular and respiratory status as well as biochemical and haematological variables. This is added to a chronic health evaluation. The admission diagnosis is then used to calculate a predicted mortality for an individual. Predicted mortality is compared to

actual mortality in a cohort of patients and a standardised mortality ratio for a unit can be calculated. This allows assessment of the therapeutic efficacy of a unit.

However, APACHE II should not be used to decide on which patients should be admitted to intensive care. This was highlighted in a document produced by a working group on admission to and discharge from intensive care and high dependency (DoH, 1996) and they conclude that APACHE II is a "probabilistic and not predictive" scoring system.

1.2.2 Clinical course of SIRS/Sepsis

Inflammatory stimuli can lead to a spectrum of outcome and it is not fully understood why two patients with equivalent injuries can have very different outcomes; one may have very little in the way of systemic upset and recover fully, the other may quickly progress to multiple organ dysfunction syndrome and death. We can group patients into one of four categories to describe their clinical course (34).

1. Little evidence of systemic reaction, organ dysfunction rarely develops.
2. Mild systemic inflammatory response syndrome and some evidence of organ dysfunction early in clinical course of disease. Dysfunction usually limited to one or two organs and rapidly resolves.

3. Massive systemic inflammatory reaction rapidly develops after initial insult. Often leads to death from profound shock within one or two days.
4. Less severe initial course but marked deterioration several days after initial insult. Multiple organ failure is common and many patients die.

Until the mid 1990s it was felt that pro-inflammatory molecules were the only substances mediating the progression of systemic inflammation to multiple organ dysfunction. Trials to reduce mortality in sepsis were attempted using anti-inflammatory agents and soluble receptors to bind the pro-inflammatory cytokines, however this did not improve mortality and may even have been harmful (35). The systemic anti-inflammatory response was clearly just as important as the pro-inflammatory response and Bone described how a pro- or anti-inflammatory predominance would manifest clinically. He described the inflammatory response at various stages of multiple organ failure (36).

Stage 1

Injury or insult induces the pro-inflammatory response locally. These mediators act to destroy damaged tissue, promote growth of new tissue and combat pathogens, antigens or neoplastic tissue. The compensatory anti-inflammatory response (CARS) is triggered to ensure the pro-inflammatory mediators do not become destructive and limits pro-inflammatory cytokine production. This is a local response and no systemic clinical signs or symptoms are seen.

Stage 2

If the injury is sufficient, pro-inflammatory and then anti-inflammatory mediators appear in the systemic circulation. Pro-inflammatory mediators recruit neutrophils, T and B cells, platelets and coagulation factors to the site of tissue injury. This cascade stimulates a compensatory anti-inflammatory response that counters the pro-inflammatory state. It is unusual to see clinical signs or symptoms and organ dysfunction is rare.

Stage 3

If regulation of the pro-inflammatory response is lost, the systemic response manifests as the clinical findings of Systemic Inflammatory Response Syndrome. We see increased systemic vascular permeability, platelet sludging, coagulation cascade activation and systemic vasodilatation. Organ dysfunction and failure may result unless homeostasis can be quickly restored. Clinically we see changes in the parameters that define a systemic inflammatory response syndrome; elevated or low white cell count, high or low temperature, tachycardia and increased respiratory rate.

Stage 4

Compensatory anti-inflammatory response can predominate causing immunodeficiency. This has been described as “immune paralysis” or “window of immunodeficiency”. Monocytes have a diminished ability to produce pro-inflammatory cytokines(37) and overwhelming infection is seen.

Stage 5

The last stage of multiple organ failure syndrome is where the body is secreting inappropriately large amounts of pro- and anti-inflammatory mediators and monocytes are deactivated. This has been called “immunological dissonance” by Bone. At this stage multiple organs require support and death is the likely outcome.

The predominant systemic response manifests clinically in one of 5 ways as described in Figure 1.1. The term MARS describes the mixed antagonists response syndrome where there are features of SIRS in patients with CARS. While treating intensive care patients with multi-organ dysfunction syndrome we are, in essence, supporting organ function while the immune system attempts to restore homeostasis.

1.2.3 Management of systemic inflammation

While many patients will resolve the inflammatory process without clinical assistance, intervention in the form of surgery or antibiotic therapy may be required. If the stimulus can be corrected surgically and the patient is fit enough, this should be undertaken. Drainage of abscesses can also be performed radiologically if general anaesthesia presents too much of a risk. Antibiotics can be administered, either as broad-spectrum cover or specific to pathogen once culture and sensitivity are known. While the patient recovers from this and until immunological homeostasis is returned, organ support may be necessary.

Two documents currently provide guidelines and standards for intensive care in the UK. "Guidelines on admission and discharge from intensive care and high dependency units" published by the Department of Health in 1996 and "Standards for intensive care units" by the Intensive Care Society inform us which patients are appropriate for intensive care:

- Patients requiring or likely to require advanced respiratory support alone (e.g. intermittent positive pressure ventilation).
- Patients requiring support of two or more organ systems.
- Patients with chronic impairment of one or more systems sufficient to restrict daily activities (co-morbidity) and who require support for an acute reversible failure of another organ system.

Categories of organ system monitoring and support are defined thus:

1. Advanced Respiratory Support
    - Mechanical ventilatory support excluding mask continuous positive airways pressure (CPAP) or non-invasive (e.g. mask) ventilation.
    - Possibility of a sudden, precipitous deterioration in respiratory function requiring immediate tracheal intubation and mechanical ventilation.
2. Basic Respiratory Monitoring and Support
    - The need for more than 40% oxygen via fixed performance mask.
    - The possibility of progressive deterioration to the point of needing advanced respiratory support (see above).
    - The need for physiotherapy to clear secretions at least two-hourly, whether via a tracheostomy, a mini-tracheostomy, or in the absence of an artificial airway.
    - Patients recently extubated after a prolonged period of intubation and mechanical ventilation.
    - Patients who are intubated to protect the airway, but needing no ventilatory support and who are otherwise stable.

3. Circulatory Support
    - Need for vasoactive drugs to support arterial pressure or cardiac output.
    - Support for circulatory instability due to hypovolaemia from any cause and which is unresponsive to modest volume replacement. This will include, but not be limited to, post-surgical or gastrointestinal haemorrhage or haemorrhage related to a coagulopathy.
    - Patients resuscitated following cardiac arrest where intensive or high dependency care is considered appropriate.
4. Neurological Monitoring and Support
    - Central nervous system depression, from whatever cause, sufficient to prejudice the airway and protective reflexes.
    - Invasive neurological monitoring.
5. Renal Support
    - The need for acute renal replacement therapy (haemodialysis, haemofiltration, or haemodiafiltration).

All aspects of intensive care medicine have been developed in recent years but there are a few interventions deserving of special mention that have changed intensive care practice and reduced mortality.

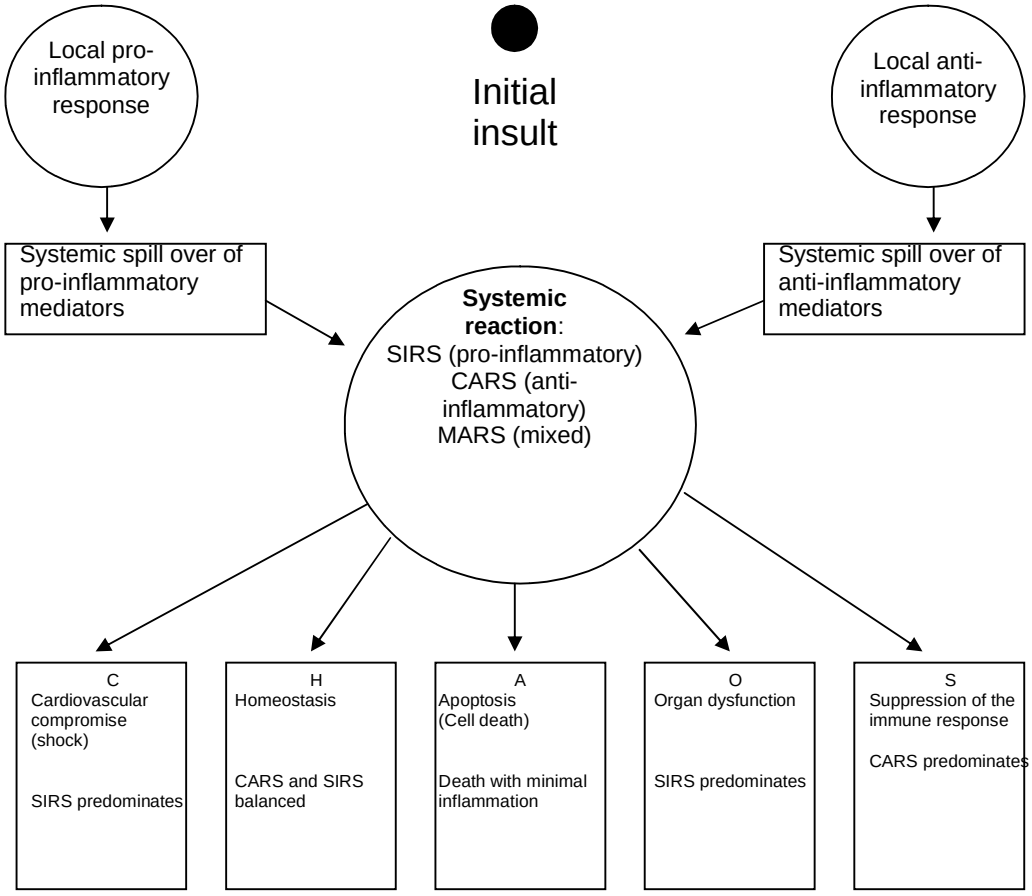
- Avoiding hypothermia by means of space blankets, forced air warming devices and blood warmers had been shown to decrease the complications of poor wound healing, exaggerated inflammatory response, ischaemic myocardial events and coagulopathy (38;39).

- Ventilator induced barotrauma has been reduced by enhancing alveolar recruitment and avoiding alveolar overdistention by lowering tidal volumes and the use of positive end expiratory pressure during ventilation (40).
- Physiological doses of hydrocortisone have been found to decrease mortality in patients with septic shock and it is patients with adrenal insufficiency who gain the most benefit (41).
- Insulin intolerance has been described for many years but it is only recently that tight control of glucose levels in all patients with sepsis has been demonstrated to decrease the incidence of septic complications and mortality (42).

As discussed above, trials where there has been administration of an anti-inflammatory agent in sepsis have not been successful as the systemic inflammatory response is not just a pro-inflammatory response. While trials of anti TNF (43) and IL-1 (44) have not shown any benefit, synthetic activated protein C appears to reduce mortality from sepsis in a subset of patients (45). Activated protein C is an endogenous protein that promotes fibrinolysis, inhibits thrombosis and inhibits inflammation. A large randomized controlled trial showed that activated protein C lowered IL-6 concentrations in the treatment arm and reduced mortality. Recombinant activated protein C is now used in everyday use in ITU to treat patients with severe sepsis and is recommended in current NICE guidelines {NICE TA84}. Recently the incidence of bleeding has been reported as higher than initially thought and the treatment itself may not be as effective as initially reported (46). Research into finding effective agents in sepsis continues.

Figure 1.1

Clinical sequelae of sepsis



From Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Critical Care Medicine 1996; 24:1125-28

1.3 **The role of the liver in the development of a systemic inflammatory response**

When tissue injury or septic foci are significantly severe there is activation of the Kupffer cells in the liver. Approximately 80% of the total body macrophages are resident in the liver (47) as Kupffer Cells. When radiolabelled E. Coli was injected intravenously into rats, 80% of the bacteria were found in the liver 5 minutes after injection (48). The Kupffer cells produce pro-inflammatory mediators, such as TNF-alpha, interleukin-1 and interleukin-6, when activated by lipopolysacccharide (LPS) (49-53) or by tissue injury(54). In infection the Kupffer cells mop up the bacteria components released by lysis mediated by cellular defence mechanisms. The Kupffer cells are activated when they recognise the attached complement and IgG with the bacterial components (55), while the pathway to activation of macrophages in tissue injury is not fully understood. The activated macrophage becomes hypermetabolic and increases its intracellular store of oxygen free radicals and other microbicidal agents as well as secreting inflammatory mediators(56;57).

Following significant tissue injury or sepsis the first pro-inflammatory mediator to be detected in the systemic circulation is tumour necrosis factor alpha (TNF-α). This cytokine is continually transcribed by Kupffer cells and allows for immediate release after inflammatory stimulus (25). TNF-α is found in serum within an hour of endotoxin infusion in human volunteers (54). This is followed by the appearance of interleukin-1 at around on hour post injury. Although IL-1 is found in high concentrations at the site of inflammatory stimulus, increased circulating concentrations are uncommon (24). At two hours after endotoxin administration a

peak in the serum levels of interleukin-6 (IL-6) is seen (54). Unlike TNF-α, IL-6 is not continuously expressed. An inflammatory stimulus results in the immediate transcription of mRNA for IL-6 in liver macrophages, and this accounts for the lag. This has been demonstrated in mice, where IL-6 mRNA levels are at their maximum following stimulation of the liver macrophages (25;58). These experiments were performed in animals or healthy volunteers given an infusion of endotoxin and probably do not give a true approximation of the timings of peaks of these cytokines in the clinical setting of tissue injury or infection. Measurement of cytokines in the post-operative setting shows TNF levels unchanged following uncomplicated surgery and a peak in systemic IL-6 at around 24 hours (59). During these initial events following infection or injury, the blood flow to the liver is increased out of proportion to blood flow to other visceral organs(9).

1.4 **The role of the liver in propagation of the systemic inflammatory response**

The predominant effect in the liver of pro-inflammatory mediators is the induction of hepatocytes to produce acute phase proteins (1). IL-6 is the most important as it orchestrates synthesis of the acute phase proteins (60), although receptors for most pro-inflammatory agents can be found on the surface of hepatocytes. Increased production of the acute phase proteins by hepatocytes can lead to an increase in serum levels by a factor of 1000(61).

The acute phase proteins (APP) are proteins that demonstrate a change in plasma concentration of at least 25% in response to an inflammatory stimulus. These proteins can show an increase in concentration (positive APP) or a decrease (negative APP).

Changes in plasma concentrations are due to increases or decreases in synthesis by hepatocytes, induced by IL-6 and an appropriate hormonal environment. In particular IL-6 is known to stimulate production of C-reactive protein. C-Reactive Protein appears to be made of 5 identical non-covalently bound subunits (62). The function of C-reactive protein in inflammation is complex and its major function is to bind phosphocholine and activate the complement system (63). It also induces the pro-inflammatory cytokines and tissue factor in monocytes (64). C-reactive protein starts to increase its systemic circulating concentration at 12 hours post injury and peaks at 48 hours in the absence of ongoing infection/injury(65;66).

C-reactive protein is the most widely used marker of the inflammatory response and has various properties that make it useful. It is usually found in the plasma at concentrations of 3mg per litre or less and values of less than 10mg per litre are regarded as clinically unimportant(67). C-reactive protein is stable in plasma (68), does not increase with age, has little or no diurnal variation (69), changes rapidly with disease and has a wide range of abnormal values (1). Elevated concentrations of C-Reactive Protein have been found to be an indicator of poor prognosis in malignant (70;71) and inflammatory conditions such as pancreatitis(72). Elevated concentrations of C-Reactive Protein are correlated with poor survival in a variety of common solid tumours and particularly in advanced disease (73). Its value in predicting severity of pancreatitis is limited by the physiological property described above, in that it does not peak until 48 hours post insult. C-Reactive Protein at 48 hours is a good indicator of severity of pancreatitis (74). This has not altered clinical practice as better prognostic indicators are available (75).

1.5 **The role of the liver in resolution of the systemic inflammatory response**

We have discussed the pro-inflammatory effects of C-reactive protein but its predominant effect may be anti-inflammatory. C-reactive protein prevents adhesion of neutrophils to endothelial cells and inhibits the generation of superoxides by neutrophils, inducing synthesis of IL-1-receptor antagonist (76). Other acute phase proteins also have anti-inflammatory effects either by protecting against reactive oxygen species (haptoglobin and hemopexin), antagonizing proteolytic enzymes (α1-protease inhibitor and α1-antichymotrypsin), or preventing generation of superoxide anion (α1-antichymotrypsin) (1;77). Two positive acute phase liver proteins are also important in tissue healing; fibrinogen causes endothelial cell adhesion, spreading and proliferation and haptoglobin stimulates angiogenesis (78).

In summary, metabolic activity in the liver is increased in injury and sepsis; Kupffer cells secrete inflammatory mediators, hepatocytes synthesize acute phase proteins and increase gluconeogenesis from muscle amino acids. To compensate for this the oxygen extraction fraction of the liver is increased (79). The liver plays a pivotal role in the maintenance of homeostasis and liver blood flow is key to this role.

1.6 Role of the liver in critically ill patients

In humans, the liver is a key organ in the development, propagation and resolution of systemic inflammation and appears to be relatively protected from failure during multi organ dysfunction syndrome. In humans, liver dysfunction is more common than

failure, however liver dysfunction is associated with an increased mortality in the critically ill patient (80-85). Liver dysfunction is usually evidenced by elevated circulating concentrations of bilirubin, transaminases or a prolonged prothrombin time (Tables 1.2 and 1.3).

Table 1.2

Studies	Patients	Criteria
Fry et al	553 postop patients	Bilirubin >34 and AST and LDH >twice normal values
Tran et al	487 ICU patients	Clinical jaundice or bilirubin >51 in the absence of hemolysis; ALT > twice normal values; hepatic encephalopathy
Hebert et al	250 septic patients	Bilirubin >60 or alk phos >350U/L
Fagon et al	1070 ICU patients	One or more of the following: bilirubin >100; alk phos >3 times normal
Bakker et al	81 septic patients	Bilirubin >34 without hemolysis and AST and ALT >80U/L
Perl et al	103 septic patients	Bilirubin >34 and alk phos, GGT, AST or ALT > twice upper limit of normal in absence of pre-existing disease
Bilirubin= micromols/litre		

From Pastor CM et al.(47)

References:

Fry et al(83), Tran et al(86), Hebert et al(82), Fagon et al(81), Bakker et al(87), Perl et al(88)

Table 1.3

		Severity Grading Score				
Studies	Patients	0	1	2	3	4
Goris et al	92 ICU patients	AST <25 and Bilirubin <34	AST 25-50 or bilirubin 34-103	AST >50 or bilirubin >103		
Carrico et al			Chemical jaundice	Clinical jaundice	Encephalopathy	
Deitch et al		Bilirubin 34-51 or LFT twice normal values (dysfunction)	Clinical jaundice with bilirubin >137 (advanced failure)			
Smail et al	163 trauma patients	Bilirubin >34	Bilirubin 68-137, PT >2s over control	Bilirubin <137, PT>4s over control		
Marshall et al	Medline database	Bilirubin<20	Bilirubin 21-60	Bilirubin 61-120	Bilirubin 121-240	Bilirubin >240
Le Gall et al	ENAS database	Bilirubin <34 and PT <3s over control	Bilirubin 34-68 and PT >3s over control	Bilirubin >68		
Vincent et al	1449 ICU patients	Bilirubin <20	Bilirubin 21-32	Bilirubin 33-101	Bilirubin 102-204	Bilirubin >204
Stevens et al	30 septic patients	Increased LDH and AST, normal bilirubin	Bilirubin 21-43	Bilirubin 44-82	Bilirubin 83-137	Bilirubin >137

Bilirubin micromols/litre, others units/litre

From Pastor CM et al(47)

Reference: Goris et al(85), Carrico et al(89), Deitch et al(90), Smail et al(91), Marshall et al(92), Le Gall et al(84), Vincent et al(93), Stevens et al(94).

1.7 **Liver Blood Flow**

1.7.1 Liver Blood Flow in Health

Anatomy

The liver receives around a quarter of the total cardiac output and this is supplied in two ways. Around a third of the total liver blood flow is arterial blood from the common hepatic artery. The remainder of the liver blood supply is received via the portal vein. This is made up from the superior mesenteric and splenic vein with a small contribution from the venous drainage of the pancreas and omentum. The inferior mesenteric vein usually joins the splenic vein before it joins the superior mesenteric vein to form the portal vein.

Histologically, these vessels main convergence is at the inlets to the hepatic sinusoids where the arterial and portal venous blood mix. In humans, a sphincter of vascular smooth muscle controls these inlets (95;96). Convergence is also found to a lesser degree before the sinusoids. Direct arterioportal anastomosis and peri-biliary capillary networks can be demonstrated (95;97).

Physiology

The liver receives 25% of the cardiac output in the resting state and between a third and a fifth of this is from the hepatic artery. Hepatic arterial blood flow and portal venous blood flow interact closely. A change in flow through one of the circuits causes the opposite change in the other circuit (98). The mechanism for this is not clear and is likely to be regulated by the pre-hepatic connections described above, however its effect is to maintain a constant liver blood flow.

Oxygen extraction is 20-35% of total body oxygen consumption and the liver has a higher oxygen extraction ratio when compared to systemic oxygen extraction (14). During exercise the blood flow to the muscles is increased at the expense of the gut and liver. The liver responds to this by increasing its oxygen extraction (79). Hypoxia superimposed on exercise can increase the oxygen extraction up to 90% indicating the liver has a great capacity to increase oxygen extraction (99).

Blood flow to the liver can be regulated by modification of the hepatic arterial or portal venous flow. Flow through the hepatic artery is proportional to arterial blood pressure and this relationship is approximately linear. Portal venous flow is modified in many ways and this includes neurological control of the vascular smooth muscle, drug effect and hormonal effect, and are best discussed split into intrinsic and extrinsic factors (98).

Intrinsic control

The intrinsic factors modifying liver blood flow include local metabolic control and myogenic control, local reflexes and locally produced vasoactive substances. This can occur in the liver, affecting mainly the hepatic arterial blood flow, or in the intestine, causing changes in the portal venous flow.

1) Metabolic control

When blood supply is not sufficient to meet the metabolic needs of a tissue, metabolic products such as hydrogen ion (100), adenosine, ATP, ADP, AMP(101) or an increase

in plasma osmolality (102) leads to local vasodilatation and an increase in blood flow. The same would appear to be happening in the gut and liver, although how this is mediated has not been identified.

2) Myogenic control

The myogenic control responds to increased vascular transmural pressure (increased venous pressure) by constriction of the arteriolar smooth muscle. This in turn increases vascular resistance and maintains a constant flow (100;103-105).
Overall adequacy of perfusion will determine which of these two control mechanisms will predominate, if perfusion is adequate an increase in venous pressure will cause arteriolar vasoconstriction by the myogenic pathway. If perfusion is poor, metabolic control will decrease vascular resistance and increase blood flow.

This autoregulation of splanchnic blood flow is not as tight as in other organs, for example the kidney where a drop in arterial pressure will result in decreased resistance in this organ such that constant blood flow is maintained. In the gut, blood flow will decrease if arterial pressure drops, despite vasodilatation, although autoregulation is better in the fed state than the fasting state (106;107).

Extrinsic control

After a meal we have an increased total liver blood flow and the mechanism for this would appear to be an increase in portal osmolality (102;108). Increased systemic osmolality (which occurs postprandially) reduces the vascular resistance in the small intestine and hepatic vascular beds, increasing blood flow in the portal vein and

hepatic artery respectively(11;108;109). Cholecystokinin is also suggested to play a role in the postprandial increase in total liver blood flow (11).

The sympathetic nervous system is the most important neural regulatory mechanism in the splanchnic blood flow. Increased sympathetic nervous activity results in a decrease in gut blood flow (110;111), mainly by acting on the arteries and arterioles rather than the veins. The aim of this reflex would be to divert blood from the gut to the heart, brain and muscles as part of the 'fight or flight' response. This reflex is not prolonged and the flow to the gut and liver recovers despite continuing sympathetic stimulation (112), termed autoregulatory escape. In the liver the action of the sympathetic nerves also causes a reduction in hepatic volume by stimulating the capacitance vessels to contract (113). This occurs slowly and acts for the duration of sympathetic stimulation, not exhibiting autoregulatory escape. The function of this mechanism would be, again, to allow redistribution of blood to other organs.

Of the many circulating hormones that affect liver blood flow, catecholamines are the most important. Arterioles exhibit both alpha and beta adrenoceptors with opposite actions. Alpha adrenoceptor stimulation results in vasoconstriction and beta adrenoceptor stimulation in vasodilatation (114). Thus the effect of a bolus of circulating adrenaline induces the same 'fight or flight' decrease in liver and gut blood flow that is seen in sympathetic stimulation. However, at lower circulating levels a vasodilatation is seen with adrenaline (11). Experimentally vasopressin(115) and angiotensin(116) have been found to be potent vasoconstrictors in the splanchnic circulation but how this affects the normal physiological regulation of liver blood flow is not fully understood. Glucagon also has a number of effects on gut and liver

vasculature, however its effects are only demonstrated at high concentrations such as those seen in sepsis and have been mentioned previously. The role of glucagon in the healthy liver is not known.

1.7.2 Liver blood flow in SIRS/Sepsis

As we have discussed earlier, systemic changes following trauma were noticed many years ago. These haemodynamics changes have been further studied and since the 1960's it has been accepted that cardiac output is raised in SIRS (117). This was first studied using pulmonary artery catheters but more recently trans oesophageal echo-Doppler (118) and peripheral lithium dilution (119) techniques have been used. This increase in cardiac output appeared to correlate with increases in serum IL-6 concentration (118).

Despite the many functions of the liver in systemic inflammation there have only been five studies where intensive care patients with SIRS were compared to controls (although one paper uses historical controls) or differing degrees of critical illness. Each paper shall be discussed and we shall also review additional literature that may help us to understand liver blood flow in systemic inflammation.

Wilmore and colleagues (120) characterised changes in hepatic blood flow and metabolism in 31 burns patients. These patients in the 1st to 3rd week post injury were classified as non-infected (8 studies), bacteraemic (8 studies) or bacteraemic with complications (5 studies). Indocyanine green (ICG) was given as a bolus with hepatic vein and radial artery sampling post injection to determine cardiac output and hepatic clearance of ICG and thus estimate hepatic blood flow. This study provided no information on hepatic arterial and portal venous flow. Patients with burns injury alone had increased hepatic blood flow, hepatic oxygen uptake and gluconeogenesis. Infection on top of this increased hepatic glucose output and in patients with bacteremia and complications glucose output fell. This study reported, for the first time, that hepatic blood flow increased following burns injury. The authors appear to have tried to differentiate between what we would now call SIRS, sepsis and MODS; and demonstrate that there were different changes in metabolism and haemodynamics of the liver for increasing severity of illness. It was also important that this study showed that gluconeogenesis only occurred in the liver, post injury, by cannulation of the renal vein in the same patients.

Aulick et al (9) assessed cardiac output, renal blood flow and splanchnic blood flow in 13 non-infected burns patients and 5 control subjects. Renal blood flow was estimated using clearance of para-aminohippurate and splanchnic flow by clearance of indocyanine green. The study reported that the renal blood flow proportion of cardiac output was not increased in burns patients compared to controls. An increase in splanchnic blood flow as a proportion of cardiac output was seen. In controls

splanchnic blood flow accounted for 19% of the cardiac output while in burns patients this proportion rose to between 20 and 25%. No details were provided on the control patients. The authors suggested that this was a liver phenomenon as the changes were not simply a reflection of cardiac output as seen with the increased renal flow in burns.

When 7 injured patients were compared to 12 patients with sepsis and stable vital signs by Dahn et al (79), cardiac output was measured and total liver blood flow was estimated. Studies were carried out at the same time of day to avoid any circadian influences. Measurements in non-septic patients were compared to those in septic patients and while no significant difference was seen in total body oxygen consumption or splanchnic flow as a fraction of cardiac output, significant increases were found in splanchnic oxygen consumption, cardiac index and venous oxygen tension. The authors felt that the most important finding of this study was that in septic patients, compared to non-septic patients, a significantly larger fraction of total body oxygen extraction was taken by the splanchnic circulation (44% vs. 30%). This paper suggested that, as splanchnic blood flow was a relatively constant 25% of cardiac output, hepatic dysfunction seen in sepsis was due to hepatic ischaemia- not from decreased blood flow, but from increased demand. No controls were studied in this paper and there was again the estimate of hepatic blood flow using a dye dilution technique.

The next study by Dahn et al (121) set out to characterize the changes in total liver blood flow in sepsis and also to assess whether different clearance methods gave a constant result. The results demonstrated a significant increase in total hepatic blood

flow in patients with sepsis compared with normal volunteers who also had liver blood flow measurements made using three different clearance indicators.

Esko Ruokonen et al(122) assessed blood flow distribution in patients with hyperdynamic septic shock and the effect of inotropes on this and oxygen transport. 10 intensive care patients with a mean APACHE II score of 13 and hyperdynamic septic shock were compared to 11 postoperative cardiac surgery patients. The control group were in the immediate postoperative phase following routine cardiac surgery and were still ventilated. Total liver blood flow and oxygen consumption was measured in the septic patients while hypotensive and during inotrope therapy. All patients with sepsis had increased total liver blood flow, compared to controls, even before inotropic support. Dopamine increased total liver blood flow in all patients but the effect of noradrenaline (norepinephrine) was not uniform; total liver blood flow increasing in three and decreasing in two patients. This paper proposed that regional blood flow changes cannot be predicted from systemic changes. It also demonstrated that during the hypotension of septic shock, total liver blood flow was markedly increased, as was oxygen extraction.

As liver blood flow would appear to be so important in sepsis and its resolution a number of studies have attempted to characterize changes in liver blood flow with various inotropic or other metabolic agents. In critically ill patients requiring inotropic support with noradrenaline, replacing noradrenaline with phenylephrine maintained systemic blood pressure but resulted in a fall in liver blood flow (123). The authors concluded that exogenous beta-adrenergic receptor stimulation determines total liver blood flow. In a similar study dopamine and noradrenaline

were found to have similar haemodynamic effects on the splanchnic circulation; however adrenaline was felt to impair total liver blood flow (124). The effect of dopexamine was studied in resuscitated septic shock patients and found it did not increase total liver blood flow. Neither was a change in liver blood flow demonstrated with an acute increase in arterial CO2 (125) or fluid optimisation (126). N-acetylcysteine increased liver blood flow and liver function in sepsis(127) and this was thought to be due to an increase in cardiac output rather than a specific effect on liver blood flow.

The above papers agree that total liver blood flow is increased in systemic inflammation when compared to control groups. They have all used hepatic vein cannulation and sampling of a clearance agent to estimate total liver blood flow. They all examined at a single point in an intensive care stay. The variability of liver blood flow in patients with sepsis was studied and the authors found that, in the 8 patients studied with stable mean arterial blood pressure considerable differences in the total liver blood flow were found, with a standard error of 31.1% at 5 minute intervals and 28.6% at 2 hours (128). No immediate clinical or prognostic value is claimed by any of the studies that estimate total liver blood flow and the placement of a hepatic venous catheter is not seen in normal clinical practice. One study has suggested that the ratio of total liver blood flow over cardiac output may be prognostic, finding liver blood flow and cardiac output correlated in non-septic patients but a lower value in sepsis. The ratio was also lower in non-survivors compared to survivors in the septic group. It is difficult to place too much value on these findings as 33 patients were studied of whom only 16 were septic (129).

Ultrasound colour Doppler/ duplex measurement of hepatic arterial and portal venous flow in critically ill patients has only been reported in one paper(130). 30 patients were compared to 12 healthy subjects. Increased total hepatic blood flow and portal venous blood flow was seen at 5 hours after the onset of sepsis but no significant difference compared to controls was demonstrated at 24 hours after onset of sepsis. No definition is given of 'onset of sepsis'. In all the other studies systemic inflammation is well established by the time measurements have been carried out. It is difficult to measure changes in blood flow immediately after the inflammatory stimulus but we can infer from other studies in the literature discussed below what is likely to occur following tissue injury/infection.

Immediate changes in blood flow are more difficult to study, as an inflammatory stimulus is usually unpredictable. The controlled trauma and tissue injury of surgery have been used in a number of studies to substitute for the inflammatory stimulus. Continual measurement of hepatic venous flow in the peri-operative period indicates flow before and immediately after inflammatory stimulus of trauma (operation). Historically a 20% decrease in hepatic venous blood flow is seen with epidural anaesthetic alone and there is a further 10% decrease with the addition of inhaled anaesthesia (131;132)**.**

Studies in patients undergoing cholecystectomy have demonstrated a decrease in hepatic venous blood flow during laparoscopic surgery to around a third of the preoperative flow. This recovers immediately after deflation of the pneumoperitoneum (132). Open cholecystectomy did not significantly alter liver blood flow in the perioperative period. This demonstrates that with modern

anaesthesia, liver blood flow changes during open surgery are not significant but pneumoperitoneum affects liver blood flow.

Other researchers have used cytokines found in high levels during inflammation to simulate systemic inflammation. In one such study we see that healthy volunteers administered a continual infusion of IL-6 demonstrate a dramatic increase in total liver blood flow (133). A mean total liver blood flow of 1300ml/min increases significantly by an hour and plateau by two hours at 1900ml/min. The plasma level of IL-6 achieved was lower than that seen in systemic inflammation but points towards cytokines being mediators of haemodynamic changes, independent of catecholamines that are known to affect blood flow and are found at higher levels in systemic inflammation. As we have discussed, in patients with a systemic inflammatory response the regulation of liver blood flow is complex and the presence of elevated levels of counter-regulatory hormones and certain cytokines are likely to be important factors in this regulation.

AIMS

The aims of the project were to:

1. Establish the effects of non-small cell lung cancer and alcoholic hepatitis on hepatic arterial and portal venous blood flow and correlate this with level of systemic inflammatory response as assessed by serum C-Reactive Protein.

2. Examine the hepatic arterial and portal venous blood flow response to a single inflammatory stimulus.

3. Evaluate longitudinal changes in hepatic arterial and portal venous blood flow in critically-ill patients during their intensive care admission.

Chapter 2: Measurement of liver blood flow in humans using the colour Doppler/ duplex ultrasound technique.

2.1 **Introduction**

Adequate blood flow is essential to the cellular function of the liver. In humans reliable techniques to measure liver blood flow are essential to ascertain whether changes in hepatic function are primarily due to altered cellular activity or secondary to changes in blood flow. A number of methods for the measurement of liver blood flow have been described in man. However in the main they have been unable to differentiate the relative contributions of hepatic arterial and portal venous flow to the total liver blood flow. Most commonly described in investigating alterations in liver blood flow in humans, whether in health or disease, is the clearance technique using markers that are cleared by the liver. Liver blood flow is then calculated by the "Fick principle," measuring marker concentration entering the liver and subtracting the concentration in the blood leaving the liver. This allows calculation of blood flow through the organ per minute; dividing total removal rate by the amount removed from each millilitre of blood that transverses the organ.

By using an infusion to obtain a constant plasma level of the marker, a steady state is achieved where the infusion rate of a marker equals the extraction rate (total removal rate). The concentration of marker before the liver is measured from arterial or peripheral venous sampling; however the concentration of marker leaving the liver can only be measured by the relatively invasive cannulation of the hepatic vein.

A number of clearance agents have been studied in the estimation of blood flow, the most common being indocyanine green. However, this may give an overestimation of hepatic blood flow as the extraction fraction of indocyanine green is reduced in sepsis

(121;134;135). This may be due to sepsis-induced changes in hepatocellular function in centrilobular locations leading to non-exchanging sinusoidal lesions and a physiological shunt (136). Galactose has also been studied and has similar problems of decreased clearance in sepsis (136-138) as well as an increased extrahepatic clearance in sepsis (137). The ideal indicator would be cleared on a single pass of the liver, not be affected by the disease state and have no extrahepatic clearance. Such an agent has not yet been found.

Other methods have been used to measure blood flow to the liver and this has been studied in the field of metastatic liver cancer from gastrointestinal origin. Dynamic flow scintigraphy is a nuclear medicine technique that uses Technetium-99 labelled colloid from the patients own blood. Gamma cameras are placed over the right liver and detect flow in the first and second eight-second period following injection. The first period was used to represent arterial flow and the second period the portal venous flow. Using this method it was suggested that patients with metastatic liver cancer had a higher proportion of total liver blood flow from the hepatic artery than patients without liver metastasis (139). Some authors have reported poor reproducibility and therefore dynamic flow scintigraphy has not been incorporated into routine clinical use (140;141). However, its use is limited to those patients who can be safely transported to the nuclear medicine department.

Following from this Miles and co-workers (142) described a method based on single-slice dynamic computerized tomography (CT) scanning. Measurements of enhancement were performed after a bolus injection of contrast medium by placing regions of interest over the liver, aorta and spleen. Estimates of hepatic arterial and

portal venous liver perfusion were obtained by dividing the maximum slope of the liver enhancement curve by the peak aortic enhancement, the splenic peak being used to separate the arterial and portal venous phases of enhancement. Significant changes in perfusion were detected in patients with various conditions, including liver metastases. However, its use is limited to those patients who can be safely transported to the radiology department.

Therefore, there is a continuing interest in measuring liver blood in the ill patient who the above techniques are in the main not suitable for making multiple and serial measurements. More recently improvements in ultrasound technology have permitted bedside, non-invasive direct measurement of blood flow in the ill patients. The introduction of colour Doppler/ duplex has enabled the measurement of hepatic arterial and portal venous blood flow in such patients (143;144). As above much of the use of this technology has focused on the prediction of hepatic metastasis in gastrointestinal cancers (145-147). While initial results from one centre were promising, again reproducibility has been a problem (148;149). However, more recently Duplex Doppler ultrasound of the hepatic artery has also been studied in hepatitis and an increased flow in alcoholic hepatitis is seen compared to viral hepatitis (150;151). Moreover, measurement of the hepatic arterial flow and portal venous flow has been found to be reproducible within and between observers (152).

The aim of the present study was to examine the reproducibility of hepatic arterial flow and portal venous flow measurements using Colour Doppler Duplex ultrasound.

2.2 **Subjects and methods**

Subjects

Intra-observer error

Seven healthy volunteers underwent repeated scanning (Table 2.1). Hepatic arterial blood flow and portal venous blood flow were measured in ml/min as described below. All measurements were taken after a minimum of 5 hours fasting at approximately the same time of day each day. The subjects' median age was 23 years (range 23-25) and male: female ratio was 2:5. Measurement values were saved directly to the ultrasound scanner to avoid unconscious bias during scans and data was analysed at the end of the procedure. Formal consent was not sought but all volunteers were medical doctors who gave oral consent and understood the investigation being performed.

Inter-observer error

Ultrasound scans of 14 patients, chosen at random, were performed by Dr John MacQuarrie and myself. Two studies were excluded by one observer due to problems locating the common hepatic artery and hence DPI values were unobtainable, a third patient was excluded due to incomplete examination. Each subject was scanned using the same Ultrasound scanner and methods as described below. As the scans were performed separately, each observer was blind to the placement of Doppler callipers and cross sectional area measurements.

Methods

Duplex/colour Doppler ultrasound of the hepatic artery was carried out using an appropriate ultrasound scanner with colour Doppler US function and a 3.5-MHz curvilinear probe. The patients were examined in the supine position and the common hepatic artery was identified along its longitudinal axis in the epigastrium by a transverse scan. The Doppler cursor was placed over the lumen of the artery, as near to the origin as possible, at the point where the artery first becomes horizontally straight. The Doppler sample volume and the beam angle are adjusted and the time average velocity was calculated over at least 4 cardiac cycles. The cross sectional area was measured at the same point as the velocity, at right angles to this. The portal vein was best viewed along its longitudinal axis with a right lateral intercostal approach and velocity was measured where this first became intrahepatic but before branching. The cross sectional area was best measured in inspiration via a subcostal approach. Three measurements were taken at each study and an average was used to calculate flow.

Blood Flow (ml/min)

= (cross sectional area) *x* (time average mean velocity) *x* (60)

= XSA (cm^2) *x* TAM (mls^{-2}) *x* 60

2.3 **Results**

Intra-observer error

Values for control of variance were calculated and an intra-observer error of around 10% was seen in hepatic arterial and portal venous blood flow (Table 2.2). These results demonstrate good reproducibility of the method in the hands of one operator.

Error in the previously published validation (152) study of the technique showed a higher variation in blood flow measurements (hepatic arterial flow 12% and 15% and portal venous flow 20% and 18%).

Inter-observer error

The mean difference (standard deviation) between the DPI values measured by both observers was -0.01 (0.07). The Intra-class correlation coefficient was 0.71, Spearman rank correlation coefficient was 0.75 (p=0.008) and conventional (Pearson) correlation coefficient was 0.70 (p=0.016), 95% Confidence Intervals were -0.05 and 0.03 (Table 2.3).

2.4 **Discussion**

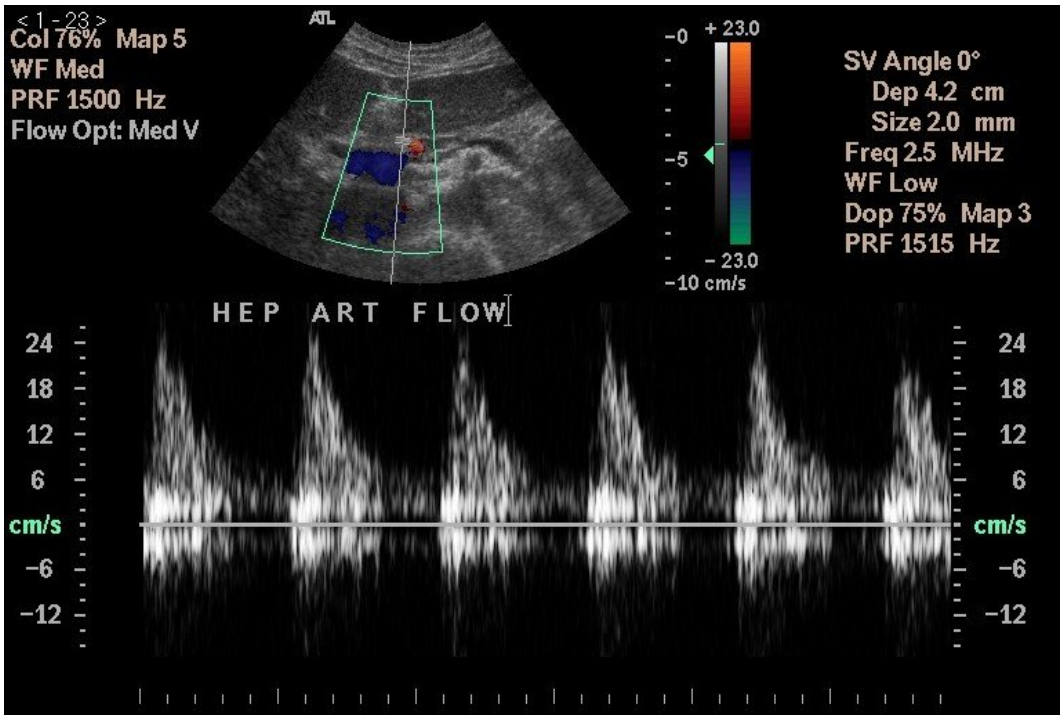
We can compare measurements in this study to total liver blood flow values than have been previously published (Table 2.4). In these studies full details of the control group are not given and we cannot assume they are completely healthy volunteers. Mean total liver blood flow in our group of healthy volunteers was 2233ml/min, which is much higher than previously published controls. The explanation for this is likely to be explained by the shorter period of fasting before scanning in the group of volunteers. It was felt that if a repeatable test could be performed, the consequence of overestimating hepatic arterial and portel venous blood flow would not influence the results of studies where patients were acting as there own controls. Previous studies have estimated total liver blood flow using different methods and direct comparisons should not be made. In the validation study by Oppo and Leen, blood flow measurements were lower in their subjects than in this study (Table 2.5), however

their population was strictly fasted for 12 hours before being studied and this may account for the differences.

The common hepatic artery arises as a branch of the coeliac trunk and is a single artery in over 80% of the population. Variant anatomy, for example a right hepatic artery arising from the superior mesenteric artery, was not identified and in the study subjects we would have expected to see a number of individuals with variant anatomy. It is accepted that measurement of the hepatic artery in these studies may have missed part of the liver blood supply, however it would have little impact on the results of the studies as we have discussed above, if flow in the same artery was repeatedly measured this would have little impact on the serial measurements.

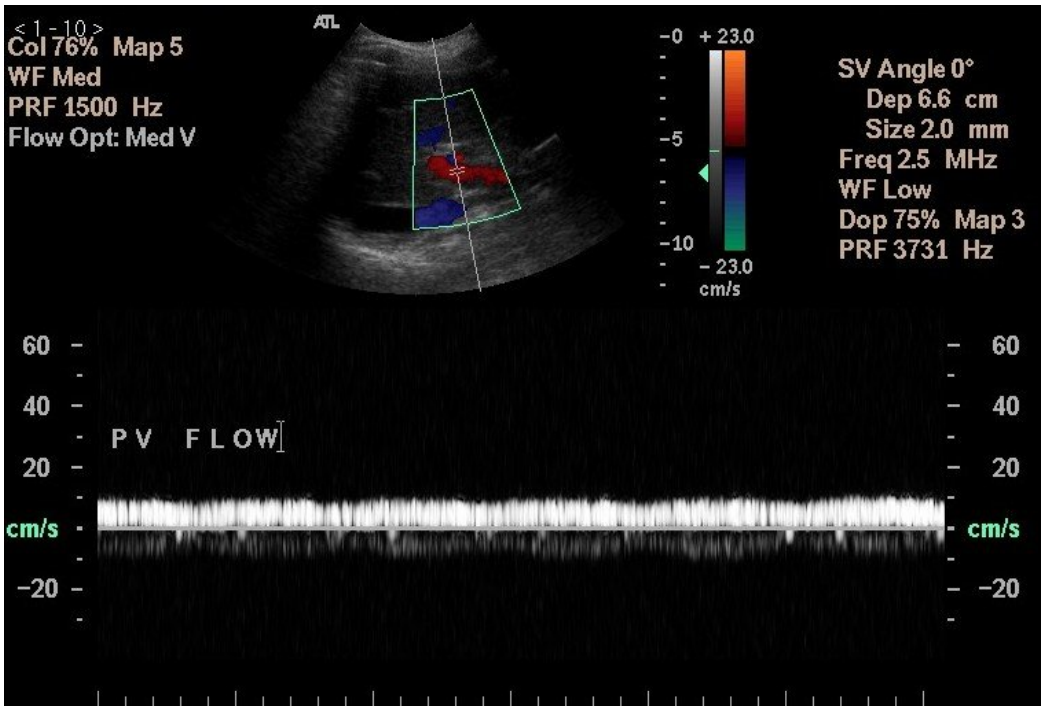
Intra-observer error was within that of the previously published validation study (152). Inter-observer error also fell within previously published values. Having validated the technique it was felt appropriate to continue the study of patient groups with inflammatory conditions. A low intra-observer error would allow us to assess changes in liver blood flow in both the hepatic artery and portal vein within cohorts where altered total liver blood flow had been demonstrated and published.

Figure 2.1 Colour Doppler / Duplex ultrasound of common hepatic artery



Typical waveform of pulsatile flow in the hepatic artery just outside the liver after the gastroduodenal artery leaves the common hepatic artery.

Figure 2.2 Colour Doppler / Duplex ultrasound of portal vein



Flatter flow in the portal vein just outside the liver before it bifurcates.

Table 2.1

Intra-observer error; repeated scans in healthy volunteers

Control	Scan No.	HA XSA	HA TAM	PV XSA	PV TAM	HABF	PVBF
A	1	0.24	43.1	1.22	24.8	621	1815
	2	0.25	36.1	1.17	19.4	542	1362
B	1	0.23	32.3	1.06	28.7	446	1825
	2	0.25	36.1	1.09	29.2	542	1910
	3	0.23	40.9	1.04	25.7	564	1604
C	1	0.35	18.8	1.45	14.8	395	1288
	2	0.36	16.4	1.40	14.4	354	1210
	3	0.35	20.1	1.49	13.4	422	1198
D	1	0.32	30.1	1.64	26.5	578	2608
	2	0.30	28.9	1.60	24.1	520	2314
	3	0.33	25.7	1.57	22.5	509	2120
E	1	0.28	34.9	1.32	19.4	586	1536
	2	0.33	36.1	1.30	17.5	715	1365
	3	0.29	36.9	1.26	19.6	642	1482
F	1	0.40		1.40	18.0		1512
	2	0.39		1.38	15.3		1267
	3	0.39		1.37	14.4		1184
G	1	0.26	36.1	1.32	20.1	563	1592
	2	0.28	28.9	1.35	18.0	486	1458
	3	0.30	34.1	1.30	28.7	614	2239

HA XSA- hepatic artery cross sectional area

HA TAM- hepatic artery time average mean velocity

PV XSA- portal venous cross sectional area

PV TAM- portal venous time average mean velocity

HABF- hepatic arterial blood flow ml/min

PVBF- portal venous blood flow ml/min

Table 2.2

Intra-observer error; control of variance in healthy volunteers

	HABF mean	Sd	CV %	PVBF mean	Sd	CV %	TLBF Mean	Sd	CV %
Subject									
A	581.07	55.96	9.63	1588.62	320.66	20.18	2169.69	376.62	17.36
B	517.22	62.96	12.17	1779.56	158.05	8.88	2296.78	143.28	6.24
C	390.38	34.15	8.75	1231.72	48.74	3.96	1622.10	59.31	3.66
D	535.66	37.03	6.91	2346.90	245.75	10.47	2882.56	281.76	9.77
E	647.72	64.42	9.95	1461.08	87.59	5.99	2108.80	25.14	1.19
F				1320.84	170.69	12.92			
G	554.16	64.61	11.66	1762.84	417.43	23.68	2317.00	475.58	20.53
Mean	537.70	53.19	9.84	1641.65	206.99	12.30	2232.82	226.95	9.79

Table 2.3
Inter-observer variation between liver blood flows measured by Doppler ultrasound.

No.	TLBF 1	TLBF 2	HAF 1	HAF 2	PVF 1	PVF 2	HA TAM 1	HA TAM 2	HA XSA 1	HA XSA 2	PV TAM 1	PV TAM 2	PV XSA 1	PV XSA 2
1	750.00	670.50	324.00	346.50	426.00	706.92	22.50	27.50	0.24	0.21	10.00	13.70	0.71	0.86
2	762.00	585.84	207.00	378.84	555.00	590.64	15.00	15.40	0.23	0.41	12.50	10.70	0.74	0.92
3	685.23	354.03	166.83	187.20	518.40	1035.72	8.30	12.00	0.34	0.26	7.20	12.60	1.20	1.37
4	602.49	359.76	86.52	273.24	515.97	1109.76	10.30	20.70	0.14	0.22	9.10	13.60	0.95	1.36
5	990.96	524.40	191.76	332.64	799.20	1382.40	18.80	19.80	0.17	0.28	14.80	18.00	0.90	1.28
6	439.20	146.52	48.60	97.92	390.60	615.60	13.50	10.20	0.06	0.16	9.30	10.80	0.70	0.95
7	915.54	386.76	193.38	193.38	722.16	722.16	29.30	29.30	0.11	0.11	10.20	10.20	1.18	1.18
8	1233.90	716.58	348.30	368.28	885.60	1098.36	21.50	19.80	0.27	0.31	18.00	16.20	0.82	1.13
9	626.40	459.00	135.00	324.00	491.40	922.32	9.00	18.00	0.25	0.30	9.00	12.60	0.91	1.22
10	1203.66	475.44	153.90	321.54	1049.76	1069.20	17.10	23.30	0.15	0.23	16.20	16.20	1.08	1.10
11	1276.38	308.04	135.24	172.80	1141.14	1350.00	9.80	14.40	0.23	0.20	14.30	18.00	1.33	1.25

TLBF Total liver blood flow (ml/min); HAF Hepatic artery flow volume (ml/min); PVF Portal venous flow volume (ml/min); HATAM Hepatic artery time-averaged velocity (cm/s); HAXSA Hepatic artery cross sectional area (cm^2); PVTAM Portal vein time-averaged velocity (cm/s); PVXSA Portal cross sectional area (cm^2).

Table 2.4

Previously published control values

	n	group	TLBF L/min/m2	TLBF 1.73L/min/m2	Measured by
Bradley 1945(153)	23	syphilis	0.87	1.5	Bromsulphalein clearance
Dahn 1990(121)	10	controls	0.74	1.28	Indocyanine green clearance
Lyngso 2002(133)	7	controls		1.3	Indocyanine green clearance
Wilmore 1980(120)		historical controls	0.63-0.85	1.1-1.5	Not stated

Table 2.5

Comparison of results with previous validation study (152)

Parameter	Observer 1	Observer 2	Table 2.1 data
HA XSA (cm2)	0.22 (0.10)	0.25 (0.13)	0.31 (0.05)
HA TAM (cm/sec)	26.3 (8.9)	24.3 (10.4)	31.5 (7.6)
HA blood flow (ml/min)	361 (267)	367 (254)	535 (94)
PV XSA (cm2)	1.24 (0.30)	1.36 (0.30)	1.34 (0.17)
PV TAM (cm/sec)	13.7 (5.0)	13.1 (4.4)	20.73 (5.2)
PV blood flow (ml/min)	1005 (407)	1052 (403)	1644 (411)
All values are mean and standard deviation			

Chapter 3： The relationship between components of liver blood flow and the systemic inflammatory response in benign and malignant disease.

3.1 **Introduction**

The liver plays an important role in the propagation, regulation and resolution of the systemic inflammatory response. Hepatocytes are recognised to be an important site of the increased gluconeogenesis and production of acute phase proteins in injury or infection. Therefore the liver is recognised to be hypermetabolic during systemic inflammation (154). The liver blood flow responses to injury or infection have not been well documented.

In malignant disease colour Doppler/duplex ultrasound of the hepatic artery and portal vein have been used to demonstrate alterations in liver blood flow in gastrointestinal cancers and breast cancers (145). In patients with benign disease such as alcoholic hepatitis it has been reported that both the diameter and the velocity of blood through the hepatic artery, and therefore blood flow, were increased compared with a control group (151).

It is now recognised that patients with advanced cancer undergo a series of pathophysiological changes, many of which are now accepted to be part of the systemic inflammatory response (1;155). Similarly, in benign disease such as alcoholic hepatitis systemic inflammatory response is recognised to play an important role in the pathophysiological of the disease (156). Both in malignant disease, such as non-small cell lung cancer, and benign disease, such as alcoholic hepatitis, the presence of systemic inflammation has been demonstrated to be associated with poorer survival (157-160).

The aim of the present study was to examine the relationship between components of liver blood flow and the systemic inflammatory response in patients with benign and malignant disease.

3.2 **Subjects and methods**

Subjects

Patients admitted to the Royal Infirmary, Glasgow with benign (alcoholic hepatitis) or malignant disease (inoperable non-small cell lung cancer) were studied. The diagnosis and aetiology of hepatitis was determined on the basis of clinical, biochemical, immunological, virological and imaging findings. Also, control subjects were recruited from patients prior to surgery for non-malignant and non-inflammatory conditions such as abdominal wall hernia, varicose veins and lower limb joint replacement. These patients underwent ultrasound examination to measure hepatic arterial and portal venous blood flow and blood was sampled for C-reactive protein measurement.

The study was approved by the research ethics committee of North Glasgow University Hospitals NHS Trust.

Liver blood flow

Hepatic arterial and portal venous blood flow measurements were carried out as previously described (see Chapter 2.2). This was validated as described in Chapter 2. Measurements of the common hepatic artery velocity and cross sectional area were made close to the origin of the vessel. No major anatomical variations were encountered.

Statistical analysis

The relationships between liver blood flow and demographic and biochemical characteristics were analysed using the Kruskal-Wallis and Mann-Whitney tests and

Spearman's rank correlation analysis as appropriate. Statistical analysis was carried out using SPSS for Windows (SPSS Inc., Chicago, USA).

3.3 **Results**

The clinicopathological characteristics of the control and patients with benign or malignant disease are shown in Table 1. All of the patients with NSCLC were inoperable and receiving palliative chemotherapy. Five patients had TNM stage IV, 4 had stage III disease and one patient had stage II disease. The latter patient was 82 and was not considered suitable for surgery. In the alcoholic hepatitis group 2 patients had Child Pugh grade B and 5 patients had C disease. The patients with alcoholic hepatitis were younger ($p<0.05$), had higher hepatic arterial blood flow ($p<0.05$) and had higher C-reactive protein concentrations ($p<0.001$).

The relationship between clinicopathological characteristics and liver blood flow is shown in Table 2. Hepatic arterial blood flow was significantly associated with disease state ($p<0.05$) and an elevated C-reactive protein concentration ($p<0.001$). Portal venous blood flow was only significantly associated with age ($p<0.05$). Total liver blood was significantly associated with an elevated C-reactive protein concentration ($p<0.05$).

Measurements for all patient groups are listed in appendix 1.

3.4 **Discussion**

The results of the present study would indicate for the first time that, in groups with increasing levels of systemic inflammation hepatic arterial blood flow is increased. In particular, it would appear that an increased hepatic arterial blood flow was associated with an elevated C-reactive protein concentration. This would suggest a role for the systemic inflammatory response in the regulation of hepatic arterial blood flow in the diseased state.

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The results of the present study are consistent with previous work which has shown increases in total liver blood flow in patients with acute illness. Wilmore and colleagues (1980) reported a stepwise increase in total liver blood flow, as calculated by indocyanine green clearance, in intensive care patients with systemic inflammatory response syndrome, patients with sepsis and patients with multi-organ dysfunction syndrome(120). However, the method used to assess liver blood flow did not provide information about the hepatic arterial and portal venous blood flow.

The effect of lesser degrees of systemic inflammation on liver blood flow are less well understood. Research in patients with malignant disease has indicated that alterations in liver haemodynamics and increase in hepatic arterial blood flow are associated with more aggressive disease, metastasis and poorer outcome (146;161;162). While systemic inflammation and particularly C - reactive protein have also been linked to histologically more aggressive cancer and poorer outcome(157;163;164), until the present work no one has shown a link between systemic inflammation and liver blood flow changes. In benign disease, alcohol induced hepatitis provokes an increase in hepatic arterial blood flow(151). This has been demonstrated to differentiate between

alcohol induced and viral hepatitis, but again, no link between systemic inflammation and liver blood flow has been previously reported. A body of work is emerging that nitric oxide is a mediator of changes in liver blood flow in alcohol induced hepatitis and accounts for the development of portal hypertension. In rats inhibition of nitric oxide synthesase leads to an increase in portal pressure and this is felt to be translatable to humans.

Studies with pro-inflammatory cytokines in cancer trials and healthy volunteers show increases in total liver blood flow which peak at 2 hours after commencement of infusion of IL-6(133). This would suggest a direct association between systemic inflammation and liver blood flow changes. However, these results do not inform us of the underlying basis of these observations. However, it may be that these changes in liver blood flow are as a result of relative hypoxia in a liver resulting in the increased production of hypoxia inducible factor which is recognised to upregulate interleukin-6 production (165) and thus C-reactive protein concentrations in the circulation (1).

The present study does not define the timing of the changes in the components of liver blood flow but does demonstrate for the first time the relative contributions to total liver blood flow. It would appear from this small study that it is the contribution from the hepatic arterial circulation that accounts for liver haemodynamic changes in systemic inflammation.

Table 1. The clinicopathological characteristics and liver blood flow in controls, non-small cell lung cancer, and alcoholic hepatitis.

	Controls (n=18)	NSCLC (n=10)	AH (n=7)	P-value
Age <65yrs	8	4	7	
65-74yrs	3	3	0	
>75 yrs	7	3	0	0.032
Sex Male	9	8	6	
Female	9	2	1	0.059
HABF (ml/min)	366	634	738	0.014
PVBF (ml/min)	1361	1335	924	0.267
TLBF (ml/min)	1759	1826	1470	0.713
C-reactive protein (mg/l)	<6 (<6-8)	16 (<6-123)	34 (<6-94)	<0.001
C-reactive protein				
≤10mg/l	18	2	1	
>10mg/l	0	8	6	<0.001

HABF, hepatic arterial blood flow; PVBF, portal venous blood flow and TLBF, total liver blood flow expressed as median. CRP, C-reactive protein; NSCLC, non-small cell lung cancer; AH, alcoholic hepatitics

Table 2. Liver blood flow in controls, non-small cell lung cancer, and alcoholic hepatitis.

	n	HABF (ml/min)	P-value	PVBF (ml/min)	P-value	TLBF (ml/min)	P-value
All patients	35	436 (98-1138)		1319 (616-2572)		1804 (714-3141)	
Age <65yrs	19	436 (98-1138)		1026 (616-2174)		1467 (714-2904)	
65-74yrs	6	511 (295-689)		1376 (674-1620)		1933 (969-2309)	
>75 yrs	10	394 (302-1115)	0.961	1398 (922-2572)	0.032	1835 (1246-3141)	0.199
Sex Male	23	458 (193-1115)		1097 (663-2572)		1804 (915-3141)	
Female	12	380 (98-1138)	0.331	1351 (616-1620)	0.424	1799 (714-2595)	0.972
Controls	18	366 (98-689)		1361 (616-2572)		1759 (714-3141)	
NSCLC	10	664 (295-1115)		1335 (663-2174)		1826 (969-2939)	
AH	7	738 (242-1138)	0.014	924 (688-1457)	0.267	1470 (1093-2595)	0.713
C-reactive protein							
≤10mg/l	21	363 (98-689)		1309 (616-2572)		1700 (714-3141)	
>10mg/l	14	705 (242-1138)	>0.001	1321 (732-2174)	0.637	1936 (1166-2939)	0.031

Results expressed as median (range). HABF, hepatic arterial blood flow; PVBF, portal venous blood flow; TLBF, total liver blood flow; CRP, C-reactive protein; NSCLC, non-small cell lung cancer; AH, alcoholic hepatitics

Chapter 4 : The relationship between hepatic arterial blood flow, portal venous blood flow and time following elective arthroplasty.

4.1 Introduction

It has long been recognised that the liver is an essential organ in the propagation, regulation and resolution of systemic inflammation(154). There is some evidence that total liver blood flow is increased as part of the systemic inflammatory response(14;117;120;122). There are also a few studies that have shown that blood flow and metabolic changes are mediated, in part, by the counter-regulatory hormones adrenaline, cortisol and glucagons (10;11;98;101) and influenced by the presence of pro-inflammatory cytokines such as interleukin-6 (16;133).

To date few studies have examined the temporal nature of the changes in liver blood flow following an inflammatory stimulus (14). Also, to our knowledge, there have been no studies, in humans which have reported the changes in hepatic arterial and portal venous components of total liver blood flow.

In order to examine the effects of the systemic inflammatory response on metabolism in humans, a number of workers have used elective surgical models such as cholecystectomy or joint replacement (65;166-168). In the case of measuring the components of liver blood flow an abdominal operation may compromise the ability to carry out ultrasound measurements and may directly influence liver blood flow. However, the elective operations of hip and knee replacement are unlikely to compromise hepatic arterial or portal venous blood flow measurements directly and do provide a standard inflammatory stimulus (15-16).

The aim of the present study was to examine the temporal relationship of hepatic arterial blood flows in patients undergoing elective hip or knee arthroplasty.

4.2 **Subjects and Methods**

Patients

Patients undergoing primary lower limb arthroplasty at the Royal Infirmary, Glasgow were studied. Prior to surgery patient age, sex and anti-inflammatory medication was recorded as well as C-reactive protein concentration.

A baseline ultrasound was performed the evening before theatre to measure hepatic arterial and portal venous flow. All patients underwent standard anaesthesia including general and epidural anaesthetic.

Immediately after transfer from theatre to the anaesthetic recovery room, the first post-operative measurement of liver blood flow was made. This was designated the zero hour scan. Further ultrasound measurements of liver blood flow were performed at two hourly intervals for the next six hours. A final scan was performed at 24 hours from the zero hour scan.

The study was approved by the research ethics committee of North Glasgow University Hospitals NHS Trust. All subjects were informed of the purpose and procedure of the study and all gave consent.

Liver blood flow

Measurements of hepatic arterial and portal venous blood flow were performed using an HDI 5000 (Philips-ATL, Bothell, WA, USA) ultrasound system with duplex-colour Doppler and a 3.5 MHz curvilinear scanhead as previously described (see

Chapter 2). Briefly, hepatic arterial and portal venous blood flows were calculated as the product of time averaged velocity and the cross sectional area of the vessel. Total liver blood flow was calculated as the sum of hepatic arterial and portal venous blood flows.

Statistical analysis

Data are presented as median and range. Data from different time periods were tested for statistical significance using the Friedman test and where appropriate, comparisons of data from different time periods were carried out using the Wilcoxon signed rank test. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

4.3 **Results**

Twenty patients were included in the study. The majority of patients were female, over the age of 70 years and had a C-reactive protein concentration in the normal range. Four patients with rheumatoid arthritis were included in the study and the remainder were osteoarthritics. Nine patients were receiving non-steroidal anti-inflammatory or COX-II inhibitors, 2 patients were on low dose prednisolone and two were taking immunosupressors (gold, sulphasalazine and methotrexate). Three patients were excluded from the analysis as they had no post-operative Doppler scans. This was due to peri-operative confusion or illness. A further 5 patients only had one other post-operative scan. Twelve patients had scans carried out at all the time-points. All patients had an uneventful perioperative period. The patient characteristics and longitudinal measurements of liver blood flow are shown in Table 1.

Hepatic arterial blood flow increased in the post-operative period ($p<0.05$), a peak at 4 hours (Figure 1). In contrast, portal venous flow fell in the post-operative period ($p<0.001$), a trough immediately post-operative (Figure 2). The net effect was a fall in total liver blood flow ($p<0.05$) in the immediate post-operative period.

Paired comparison of pre-operative and 24 hour hepatic arterial flows showed no difference ($p=0.753$) and therefore hepatic arterial flow returned to pre-operative values. In contrast, paired comparison of pre-operative and 24 hour portal venous flows showed that portal venous flow fell ($p=0.046$) and therefore portal venous flow had not returned to pre-operative values.

Liver blood flow measurements for each patient are listed in appendix 2.

4.4 **Discussion**

The results of the present study show, for the first time, that there is an immediate post-operative reduction in portal venous blood flow followed by an increase in hepatic arterial blood flow resulting in a reduction of total liver blood flow in patients following elective knee arthroplasty.

The basis of these observations is unclear. However, the classical neuro-endocrine mediated 'fight or flight' response to tissue injury is known to occur rapidly and is thought to divert blood away from tissues such as the splanchnic organs which are not required for this response. The results of the present study confirm that there is indeed a reduction in total liver blood flow.

However, there was also an increase in hepatic arterial blood flow following tissue injury. The mechanism by which hepatic arterial blood flow is increased is not clear. There are a number of possible explanations for later transient increase in hepatic arterial blood flow.

It could be due to the technical aspects of the operative procedure itself. However, modern anaesthesia is not thought to affect liver blood flow (132). This has been studied in patients undergoing laparoscopic surgery where the pneumoperitoeum was considered to have the potential to compromise splanchnic blood flow and thus liver function in the post-operative period. It has been demonstrated that in elderly patients undergoing laparoscopic surgery there is a decrease in total liver blood flow that is not demonstrated in the younger patients or at open surgery. Thoracic epidurals have been demonstrated to reduce total liver blood flow, lower epidurals such as these

patients received have not shown this effect on liver blood flow (132). It could be simply a passive reactive response to a fall in portal venous blood flow. Venous transmural pressure feeds back to the arterioles in the liver decreasing arterial resistance and increasing blood flow (100). As discussed in the introduction the strongest influence on liver blood flow is the metabolic intrinsic control. Increased products of metabolism will act locally to vasodilate and increase blood flow (100;101). Feeding is demonstrated to increase liver blood flow (99) but in this study all patients were fasting during the first 6 hours and its influence is controlled in this study.

Alternatively, the increase in hepatic arterial blood flow may be as part of the systemic inflammatory response to injury. For example, following an inflammatory stimulus there is good evidence that the liver becomes hypermetabolic (1) and has an increased demand for oxygen which an increase in hepatic arterial flow would provide. Also, it is of interest that in the profound systemic inflammatory response of the critically-ill patients increases in total liver blood flow have been reported (79;120-122). Further evidence of the role of the systemic inflammatory response is that an infusion of IL-6 into healthy volunteers was associated with an increase in total liver blood flow (11). Therefore, it would appear that the increase in hepatic arterial blood flow seen in the present study may be a systemic inflammation driven response.

Table 1 Liver blood flow following lower limb arthroplasty.

	Pre-op	Post-op Immediate	Post-op 2hr	Post-op 4hr	Post-op 6hr	Post-op 24hr	Pre-op- 24hr Friedman
	(n= 20)	(n=17)	(n=13)	(n=12)	(n=12)	(n=13)	(P-value)
Age	72 (40-83)						
Sex (M:F)	8:12						
Disease (OA:RA)	16:4						
C-reactive protein (mg/l)	6 (6-6)						
HABF (ml/min)	412 (233-687)	432 (262-640)	484 (262-667)	546 (275-899)	412 (259-833)	469 (253-689)	0.038
PVBF (ml/min)	1419 (869-2798)	979 (454-1413)	1251 (708-1555)	1209 (553-2183)	1333 (810-1952)	1424 (810-1771)	<0.001
TLBF (ml/min)	1898 (1102-3423)	1538 (762-1965)	1756 (971-2222)	1734 (1224-2822)	1760 (1069-2785)	1830 (1063-2428)	0.012

OA osteoarthritis, RA rheumatoid arthritis, HABF, hepatic arterial blood flow; PVBF, portal venous blood flow and TLBF, total liver blood flow expressed as median (range), C-reactive protein expressed as median (IQ range)

Figure 1. Pre- and post-operative hepatic arterial blood flow measurements in patients undergoing lower limb arthroplasty

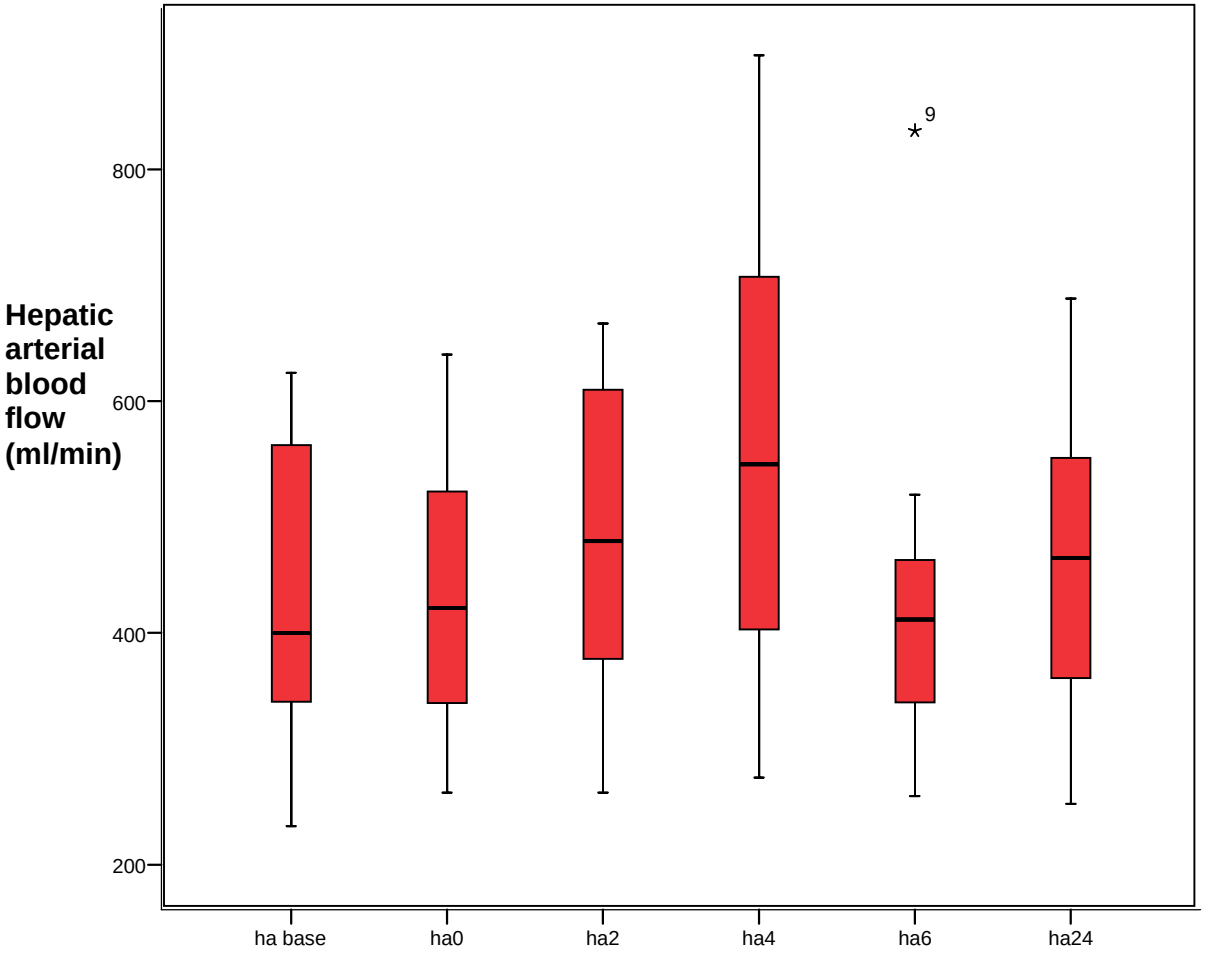

Figure 1 demonstrates changes in median hepatic arterial blood flow in ml/min (y-axis) over the time points in the study (x-axis). Time points are ha base= pre-operative, ha0= immedialty post-operative, ha2= 2 hours post-op, ha4= 4 hours post-op, ha6= 6 hours post-op and ha24= 24 hours post-op.

A peak in hepatic arterial blood flow is demonstrated at 4 hours post-operatively.

Figure 2. Pre- and post-operative portal venous blood flow measurements in patients undergoing elective knee arthroplasty

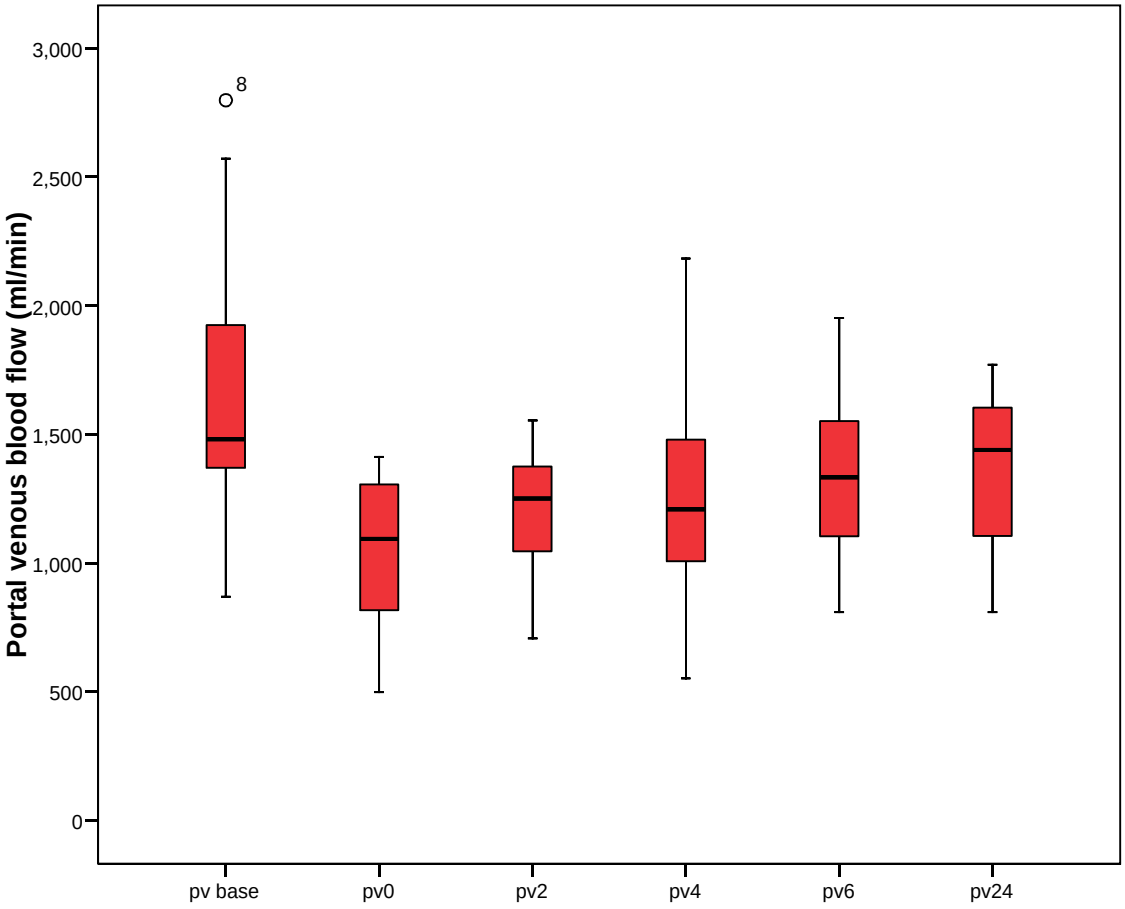

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Figure 2 demonstrates changes in median portal venous blood flow in ml/min (y-axis) over the time points in the study (x-axis). Time points are pv base= pre-operative, pv0= immedialty post-operative, pv2= 2 hours post-op, pv4= 4 hours post-op, pv6= 6 hours post-op and pv24= 24 hours post-op.

Portal venous blood flow falls immediately post-operatively and then gradually recovers over time.

Chapter 5 : Longitudinal study of hepatic arterial and portal venous blood flow in the critically ill patient.

5.1 **Introduction**

In chapters 3 and 4 we have demonstrated that an increase in liver blood flow in a variety of patient groups was associated with the presence of a systemic inflammatory response and these changes were predominantly influenced by an increase in the hepatic arterial component of the total liver blood flow. As described in the introduction (Chapter 1), systemic inflammation can be present to a degree that it compromises homeostasis and organ function and therefore organ support is required. At this extreme of systemic inflammation, patients require support of their multi-organ dysfunction syndrome in the critical care setting.

As described in the introduction (Chapter 1) the liver plays a crucial role in the regulation of the systemic inflammatory response and therefore, its appropriate functioning becomes essential for patient outcome. It has long been recognised that liver dysfunction in intensive care patients is associated with poor outcome and blood flow to the liver is therefore of great importance (80-85). The relative inaccessibility of the portal vein and hepatic artery to non-invasive monitoring has resulted in fewer studies in this area than would be perhaps expected. The few human studies described in the introduction (Chapter 1) indicate that total liver blood flow is increased in the intensive care setting (9;79;120-122), but give no information on the components of the total liver blood flow or how this changes over the course of the critical illness.

On the basis of the results obtained in Chapters 3 and 4 it might be anticipated that there would be an increase in hepatic arterial blood flow in intensive care patients and that the increase in hepatic arterial blood flow would reflect the magnitude of the systemic inflammatory response. Therefore, the aim of the present study was to

examine the longitudinal relationship between hepatic and portal venous blood flows and the systemic inflammatory response in patients with critical illness.

5.2 **Subjects and Methods**

Patients

Patients (n= 31) admitted to the intensive care unit at Glasgow Royal Infirmary over a one and a half year period were considered for inclusion in the study. The patients recruited were predominantly male (58%), general and vascular surgical patients (52%), with only 4 (13%) medical patients (Table 1).

Patients with pre-existing liver dysfunction, metastatic liver disease, or who had burns or a wound over the right upper quadrant of the abdomen and where scanning would be uncomfortable or an infection risk were excluded from study.

The study was approved by the local research and ethics committee at Glasgow Royal Infirmary.

Methods

Patients underwent ultrasound assessment of their hepatic arterial and portal venous blood flow at daily intervals, where clinically practical, during their intensive care stay. Hepatic arterial, portal venous blood and total liver flow was assessed as previously described in Chapter 2.

Admission demographics including APACHE-II score and predicted mortality were recorded. Serum C-reactive protein and the degree of organ support and was assessed daily. ITU and hospital outcome data was collected.

Statistics

Comparisons of baseline characteristics of patient groups were performed by Chi-square or Mann-Whitney U test as appropriate. Paired comparisons between different study days was performed by Wilcoxon signed rank test. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

5.3 **Results**

Baseline measurements of liver blood flow, organ support and the systemic inflammatory response in control and critically-ill patients are shown in Table 2. Thirty-one intensive care patients were recruited with a total of 202 measurements of hepatic arterial and portal venous blood flow performed. Control and critically-ill groups were similar in terms of age and sex. The median APACHE II score on admission was 21 and predicted survival was 35%. In the critically-ill patient group hepatic arterial blood flow ($p<0.05$) and C-reactive protein concentrations ($p<0.001$) were significant higher compared with controls. In contrast, portal venous blood flow was similar to controls ($p=0.147$). The median C-reactive protein concentration in the critically-ill group was 103mg/l.

When liver blood flow measurements at the peak systemic inflammatory response in the critically-ill group were compared with control group (Table 3), there was, in addition to an increase in hepatic arterial blood flow ($p<0.001$), an increase in total liver blood flow ($p<0.01$). The median C-reactive protein concentration at the peak of the inflammatory response in the critically-ill group was 168mg/l.

Longitudinal measurements of liver blood flow, organ support and the systemic inflammatory response in critically-ill patients are shown in Tables 4a and 4b. Due to the nature of the changing critically-ill population studied (patients entered the study at different times due to clinical imperative and left the study at different times due to death or discharge from the intensive care) comparisons were carried out between the average measurements in one 24 hour period, compared to the next 24 hour period for days 0-5 (Table 4a). For the subsequent measurements up to day 13, comparisons

were carried out between the average measurements in one 48 hour period, compared to the next 48 hour period (Table 4b).

In the first five 24 hour periods (Table 4a) there were no significant changes in liver blood flows. In contrast, C-reactive protein was significantly increased from day 0 to day 1 and fell significantly from day 3 to day 4.

In the second four 48hour periods (Table 4b) there were increases in hepatic arterial ($p<0.05$), portal venous ($p<0.05$) and total liver blood flows ($p<0.05$) between days 10/11 and 12/ 13.

All scans performed in intensive care patients (n=202) were used to assess for correlation between inflammatory status and blood flows (Figures 1-3). There was a trend towards a positive association between hepatic arterial blood flow and C-reactive protein ($rs= 0.074$, Figure 1a). In contrast, there was no association between portal venous blood flow and C-reactive protein ($rs>0.001$, Figure 2a), or C-reactive protein and total liver blood flow ($rs= 0.013$, Figure 3)

5.4 **Discussion**

In the present study hepatic arterial flow, on admission, was higher in critically-ill patients compared with age and sex matched controls. Furthermore, it was shown that, at the peak of their systemic inflammatory response, there was an increase in hepatic arterial blood flow in patients with critical illness in addition to the increase in total liver blood previously reported (9;79;120-122). With respect to the longitudinal measurements carried out in the patients with critical illness the results were less clear cut since, following admission, there were fluctuations in both blood flow measurements and the systemic inflammatory response. Nevertheless, including all blood flow and C-reactive protein values in the first two weeks of study (n=140) there was a trend towards a significant positive association between hepatic arterial blood flow and C-reactive protein but not portal venous blood flow and C-reactive protein. Therefore, the results of the present study are consistent with the concept that the systemic inflammatory response is an important mediator of hepatic arterial and total liver blood flow in patients with critical illness.

In the introductory chapter (Chapter 1) we discussed both the intrinsic or extrinsic factors controlling liver blood flow. However, in the critically-ill patient with the loss of homeostasis it is likely that a number of other factors will impact on the components of liver blood flow. For example, there is an additional metabolic demand placed on the liver as protein synthesis, cytokine production and gluconeogenesis are all stimulated as part of the systemic inflammatory response. Also, there is likely to be increased metabolic activity in the liver resulting in accumulation of metabolic products (hydrogen ions, ADP, ATP) and these are potently vasoactive causing local vasodilatation and increased blood flow (100;101).

Extrinsic factors such as endogenous and exogenous catecholamines affect liver blood flow, high levels of adrenaline leading to the fight or flight effect and diverting blood away from the gastrointestinal tract to the more immediately important organs, low levels causing vasodilatation and increased liver blood flow (11). Increases in liver blood flow are also associated with increased gastro-intestinal intraluminal osmolality (102;108) and therefore it is of interest that all the critically ill patients were fed from the day of admission to ITU.

Therefore, due to the complexity of factors that may alter liver blood flow in patients with critical illness it is not possible to attribute the blood flow changes to any individual factor with confidence. However, it of interest that there was a direct association of hepatic arterial, but not portal venous, blood flow and the systemic inflammatory response, as evidenced by elevated C-reactive protein concentrations. Moreover, the results of the present study are consistent with previous two Chapters and implicate the systemic inflammatory response as a driver of hepatic arterial blood flow in health and disease.

Table 1a. Admission characteristics of study patients

	Reason for admission	Age	Sex	APACHE II	Predicted mortality
1	Post op, small bowel obstruction	29	F	10	3.3
2	Post op, perforated colon	78	M	28	77.5
3	Post op, small bowel obstruction	53	M	11	5.0
4	Post op, elective AAA, pneumonia	73	F	15	21.0
5	Post op, elective AAA	65	M	13	5.0
6	Post op, elective facial cancer surgery	69	M	16	11.2
7	Post op, emergency AAA, renal failure	64	M	28	78.6
8	Sepsis, asystolic arrest	77	M	31	73.3
9	9% burns- face and hands	46	M	7	3.3
10	Post op, emergency AAA	70	F	21	23.8
11	Post op, necrotising fasciitis	31	F	14	26.8
12	Aspiration pneumonia	49	F	13	16.5
13	Post op, emergency AAA, respiratory and renal falure	77	M	21	38.9
14	Post op, congenital neck deformity	21	M	10	5.0
15	Pancreatitis, respiratory failure	75	F	26	50.7
16	COPD and pneumonia	66	F	30	49.3
17	Post op, perforated colon	37	M	19	48.0
18	Post op, small bowel obstruction	55	F	18	28.9
19	Post op, drainage subdural haematoma	67	M	26	35.2
20	Left ventricular failure and arrest	65	F	25	62.9
21	Post op, elective AAA	84	M	21	57.0
22	Post op, pulmonary lobectomy and MI post operatively	64	M	20	30.0
23	Post op, submandibular abscess	43	M	27	38.6
24	Pancreatitis	29	M	26	68.6
25	Post op, large bowel obstruction	38	F	14	30.8
26	Post op, completion proctectomy, intra op. bleed	77	F	13	16.4
27	Pancreatitis	75	F	27	71.6
28	Post op, bleeding duodenal ulcer	82	F	22	42.1
29	Post op, bleeding duodenal ulcer	71	M	34	80.7
30	Post op, osteosarcoma mandible	30	M	13	16.5
31	Post op, redo vascular surgery (ax bi fem graft)	72	M	33	78.6

Table 1b Summary of Admissions by Type

	Age (yrs)	Sex (M:F)	APACHE II	Predicted mortality (%)
Surgical (n=27)	65 (21-84)	17: 10	10 (7-34)	30.8 (3.3-80.7)
Medical (n=4)	66 (49-77)	1: 3	27.5 (13-31)	56.1 (16.5-73.3)

Values- median (range)

Table 2. Baseline measurements of liver blood flow, organ support and the systemic inflammatory response in control and critically-ill patients

	Controls, (n=18)	Critically-ill (n=31)	P-value
Age	72 (36-87)	65 (21-85)	0.237
Sex (M:F)	9:9	18:13	0.584
APACHE II		21 (7-34)	
Organs supported (n)		1 (0-3)	
HABF (ml/min)	366 (98-689)	542 (130-1472)	0.029
PVBF (ml/min)	1361 (616-2572)	1176 (587-2590)	0.820
TLBF (ml/min)	1759 (714-3141)	1996 (730-4040)	0.213
C-Reactive Protein (mg/l)	<6 (<6-8)	103 (22-390)	<0.001

Values- median (range)

HABF- hepatic arterial blood flow, PVBF- portal venous blood flow, TLBF- total liver blood flow.

Table 3. Measurements of liver blood flow, organ support at the peak systemic inflammatory response in critically-ill patients

	Controls, n=18	ITU patients, n=31	P
Age	72 (36-87)	65 (21-85)	0.237
Sex (M:F)	9:9	18:13	0.584
Organs supported (n)		1 (0-3)	
HABF (ml/min)	366 (98-689)	648 (202-1472)	<0.001
PVBF (ml/min)	1361 (616-2572)	1494 (644-2588)	0.147
TLBF (ml/min)	1759 (714-3141)	2308 (1102-4039)	0.003
C-Reactive Protein (mg/l)	<6 (<6-8)	168 (45-390)	<0.001

Values- median (range)

HABF- hepatic arterial blood flow, PVBF- portal venous blood flow, TLBF- total liver blood flow.

Table 4a. Longitudinal measurements of liver blood flow, organ support and the systemic inflammatory response in critically-ill patients.

	Day 0-1	Day 1-2	Day 2-3	Day 3-4	Day 4-5
N	7, 10	10, 12	12, 14	14, 17	17, 15
Pairs	6	6	7	12	10
Organs supported (mean n)	1 (0-3), 1 (0-3)	1 (0-3), 1 (0-3)	1 (1-3), 1 (1-3)	1 (1-3), 1 (1-3)	1 (1-3), 1 (1-2)
HABF	379 (282-1162), 562 (405-1472)	562 (405-1472), 575 (201-1432)	575 (201-1432), 638 (369-1436)	638 (369-1436), 500 (209-1219)	500 (209-1219), 647 (233-1301)
PVBF	1305 (798- 2099), 1386 (811-2568)	1386 (811-2568), 1141 (587-2590)	1141 (587-2590), 1145 (643-2097)	1145 (643-2097), 1445 (659-2158)	1445 (659-2158), 1746 (783-2493)
TLBF	2062 (1350- 2466), 2007 (1293- 4040)	2007 (1293- 4040), 1763 (1048- 3393)	1763 (1048- 3393), 1698 (1012- 3533)	1698 (1012- 3533), 1996 (981- 2880)	1996 (981- 2880), 2483 (1042-3794)
CRP (mg/l)	84 (22-390), 164 (22-267) *	164 (22-267), 173 (45-337)	173 (45-337), 129 (59- 292)	129 (59- 292), 107 (42-232) **	107 (42-232), 114 (24- 266)

Values- median (range)

HABF- hepatic arterial blood flow, PVBF- portal venous blood flow, TLBF- total liver blood flow CRP C-reactive protein,

*$p<0.05$, **$p<0.005$

Table 4b. Longitudinal measurements of liver blood flow, organ support and the systemic inflammatory response in critically-ill patients.

	Day 4/5 – 6/7	Day 6/7 – 8/9	Day 8/9 – 10/11	Day 10/11- 12/13
N	22, 10	10, 12	12, 11	11, 11
Pairs	8	7	8	6
Organs supported (mean n)	1 (1-2), 1 (1-2)	1 (1-2), 1 (0-2)	1 (0-2), 1 (0-2)	1 (0-2), 1 (0-2)
HABF	664 (209-1300), 573 (294-1015)	573 (294-1015), 591 (277-871)	591 (277-871), 465 (292-815)	465 (292-815), 659 (360-937) *
PVBF	1510 (752-2495), 1334 (889-1793)	1334 (889-1793), 1311 (691- 1966)	1311 (691- 1966), 1127 (720- 2153)	1127 (720- 2153), 1462 (1134- 2095) *
TLBF	2238 (1012- 3794), 2050 (1357- 2700)	2050 (1357- 2700), 1836 (1069- 2837)	1836 (1069- 2837), 1670 (1310- 2491)	1670 (1310- 2491), 2091 (1742- 3031) *
CRP	118 (36-266), 101 (55-214)	101 (55-214), 172 (36-231)	172 (36-231), 91 (13-264)	91 (13-264), 94 (41-218)

Values- median (range)

HABF- hepatic arterial blood flow, PVBF- portal venous blood flow, TLBF- total liver blood flow CRP C-reactive protein,

* $p<0.05$

Figure 1a. Hepatic arterial blood flow and inflammation in all patients

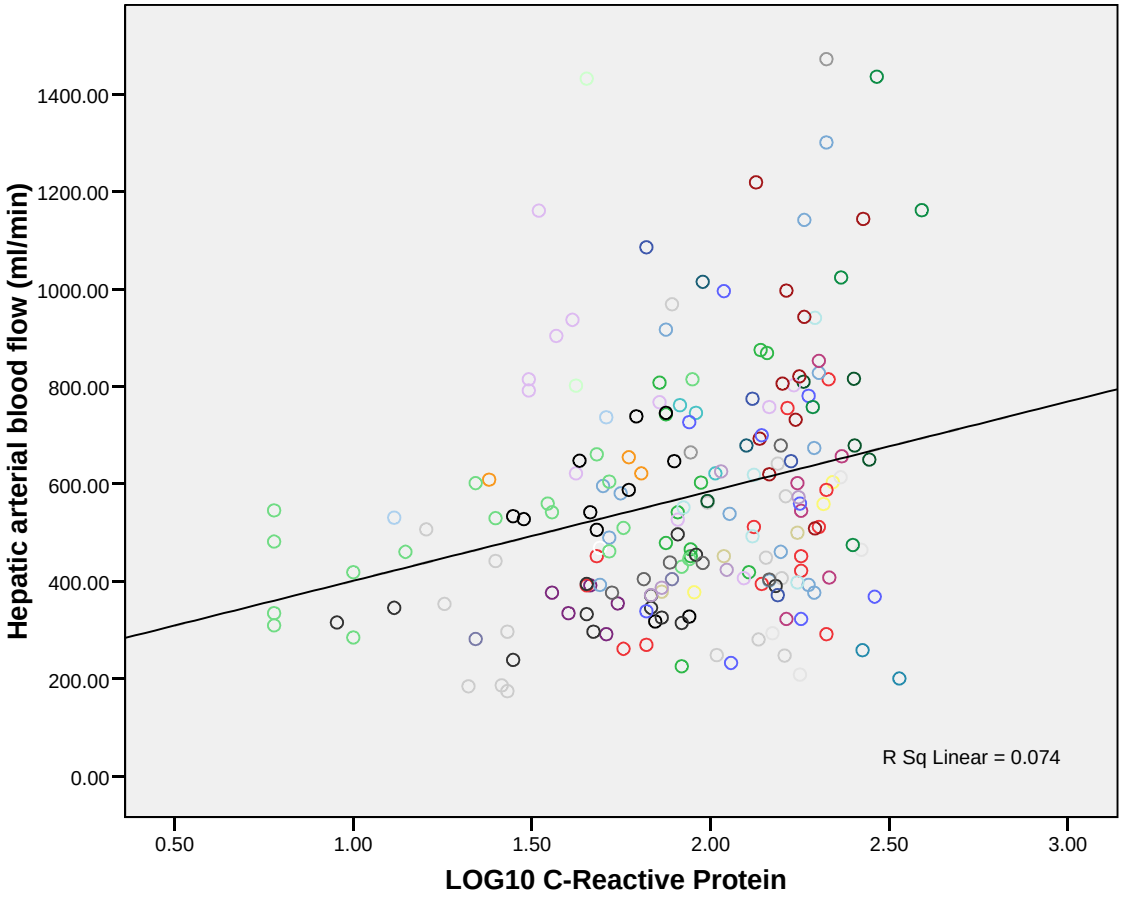

Figure 1a demonstrates hepatic arterial blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in all study patients. Individual patients are coded in different colours and the overall line of best fit is displayed.

Figure 1b. Hepatic arterial blood flow and inflammation in survivors

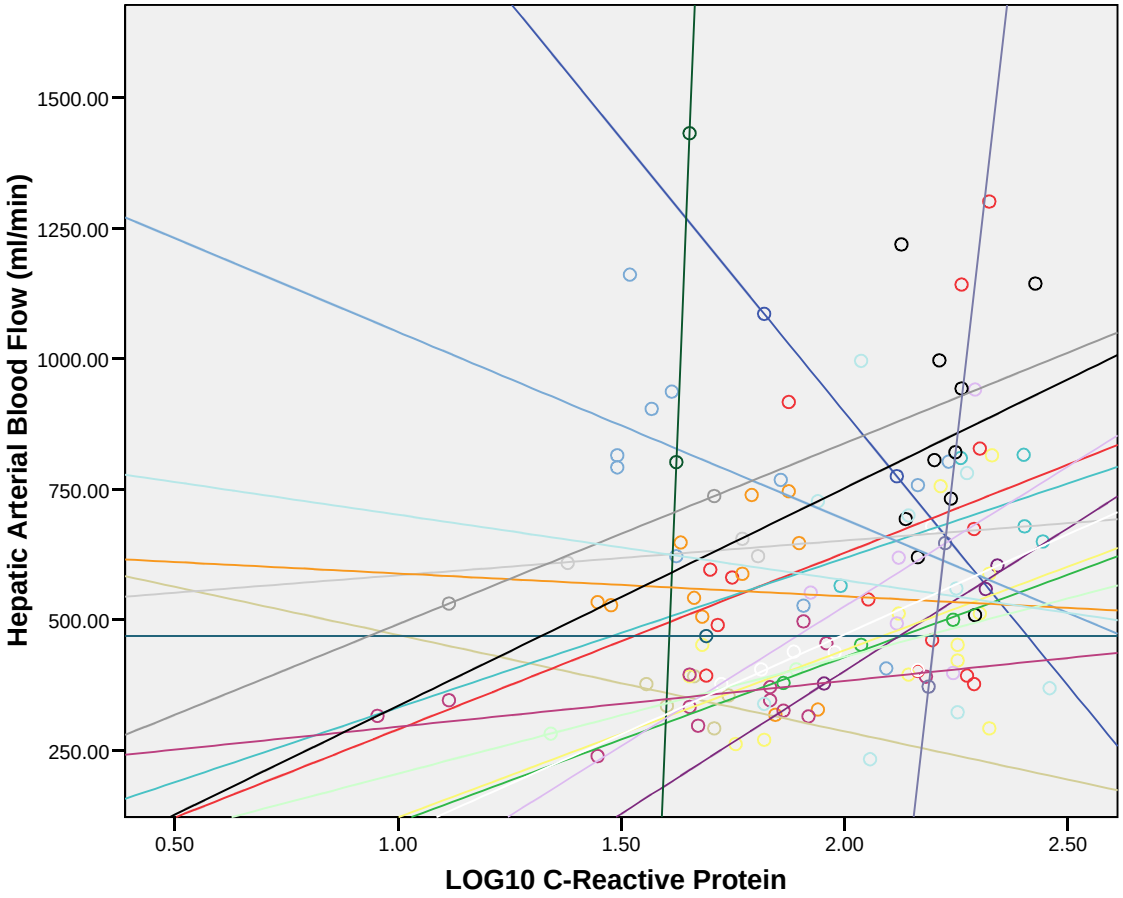

Figure 1b demonstrates hepatic arterial blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in survivors. Individual patients are coded in different colours and individual lines of best fit are displayed.

Figure 1c. Hepatic arterial blood flow and inflammation in non-survivors

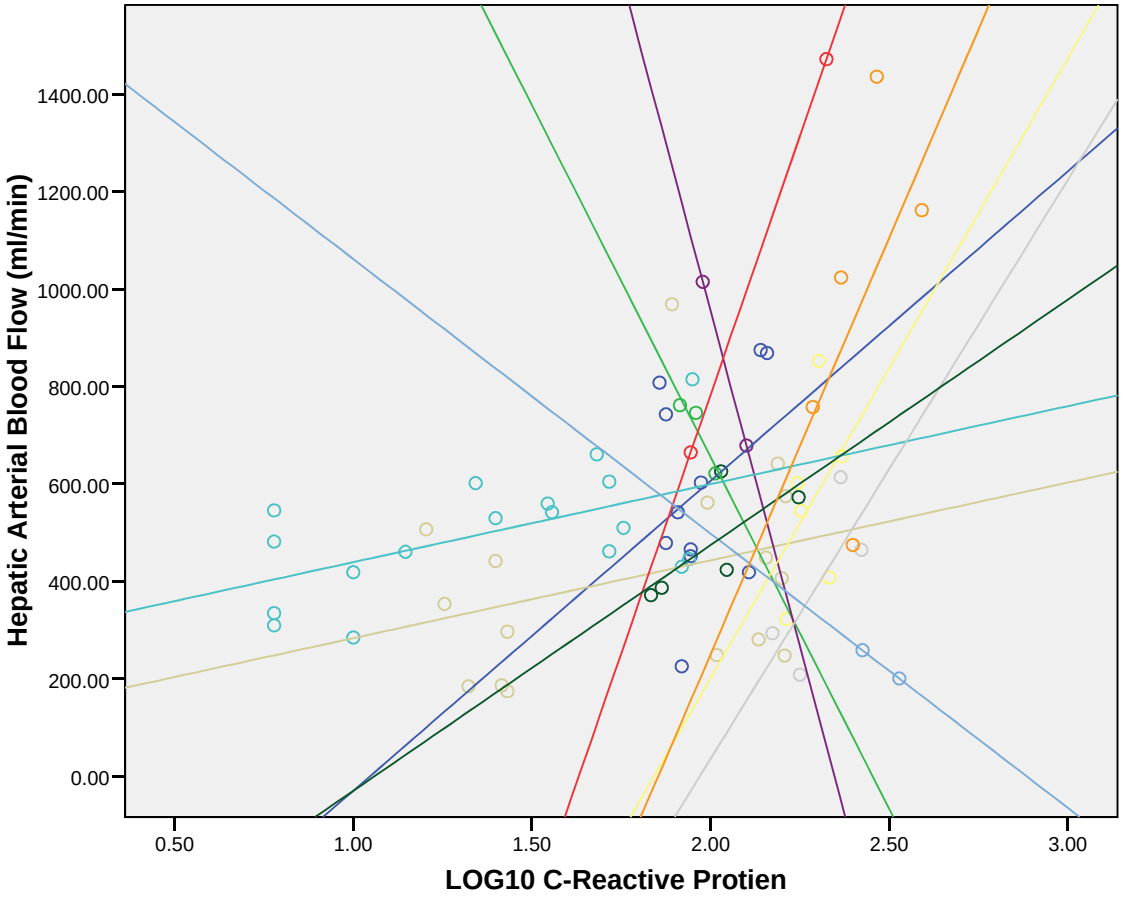

Figure 1c demonstrates hepatic arterial blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in non-survivors. Individual patients are coded in different colours and individual lines of best fit are displayed.

Figure 2a. Portal Venous Blood Flow and inflammation in all patients

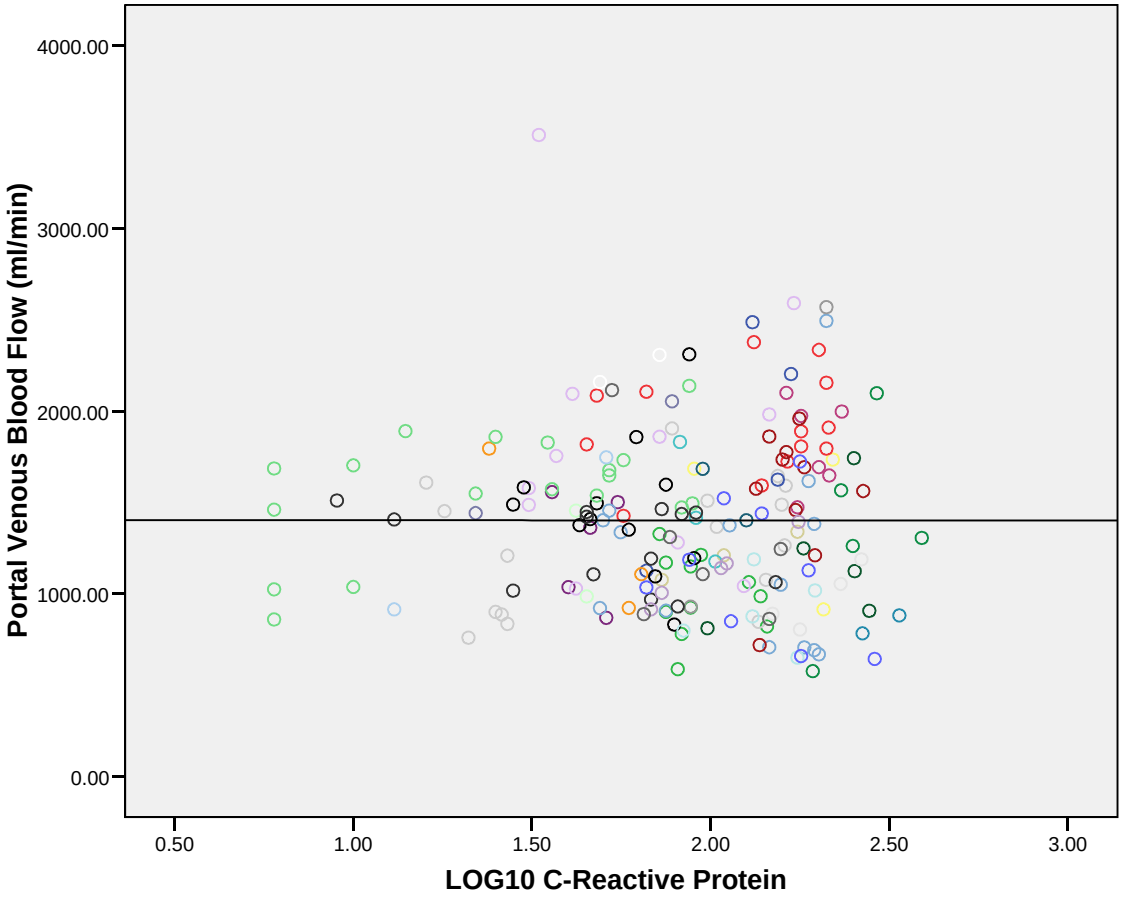

Figure 2a demonstrates portal venous blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in all study patients. Individual patients are coded in different colours and the overall line of best fit is displayed.

Figure 2b. Portal Venous Blood Flow and inflammation in survivors

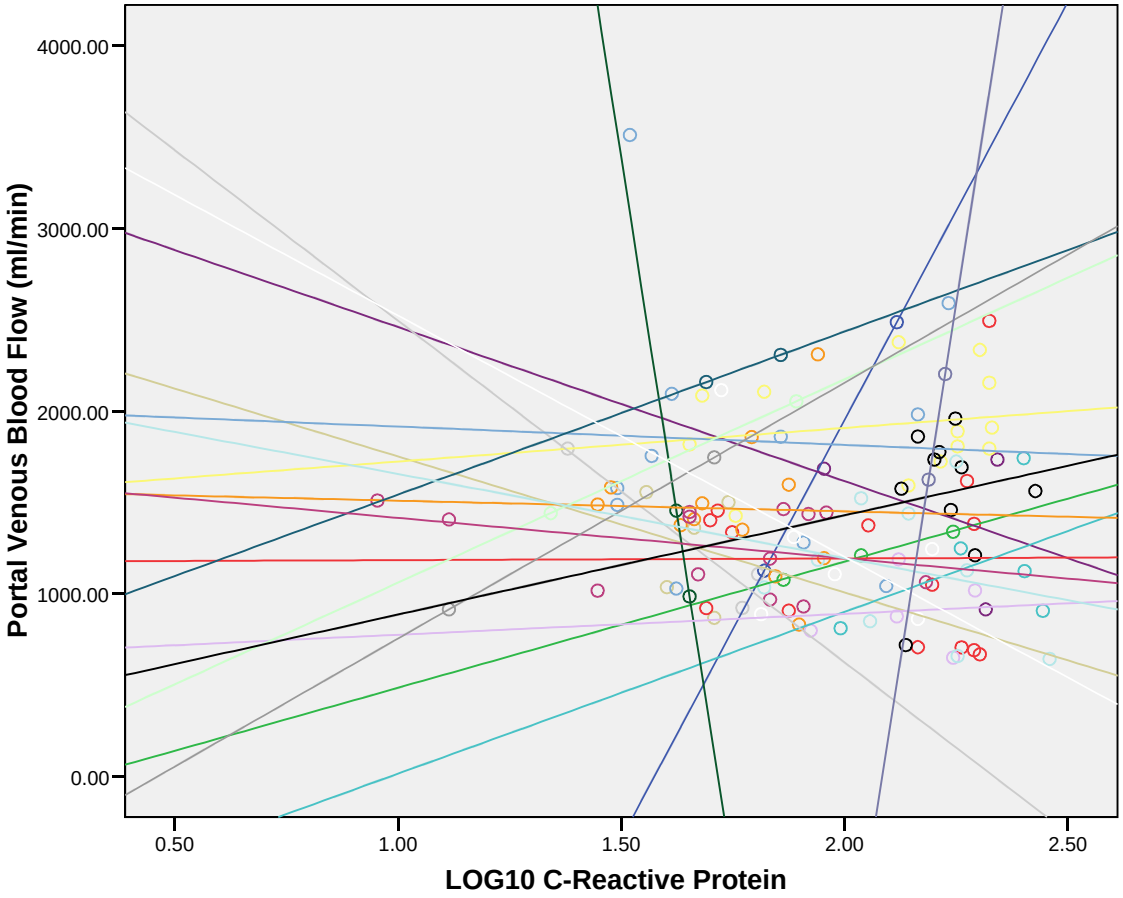

Figure 2b demonstrates portal venous blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in survivors. Individual patients are coded in different colours and individual lines of best fit are displayed.

Figure 2c. Portal Venous Blood Flow and inflammation in non-survivors

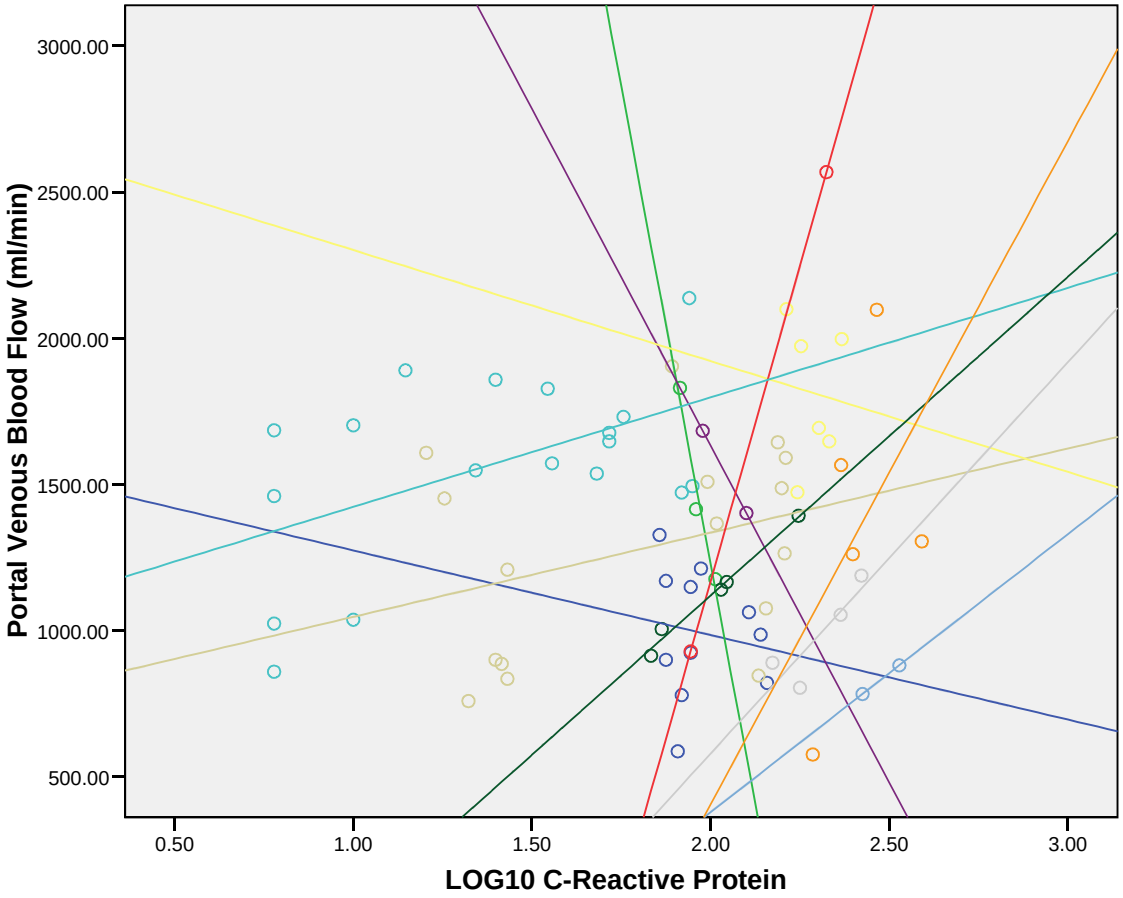

Figure 2c demonstrates portal venous blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in non-survivors. Individual patients are coded in different colours and individual lines of best fit are displayed.

Figure 3 Total Liver Blood Flow and Inflammation in all patients

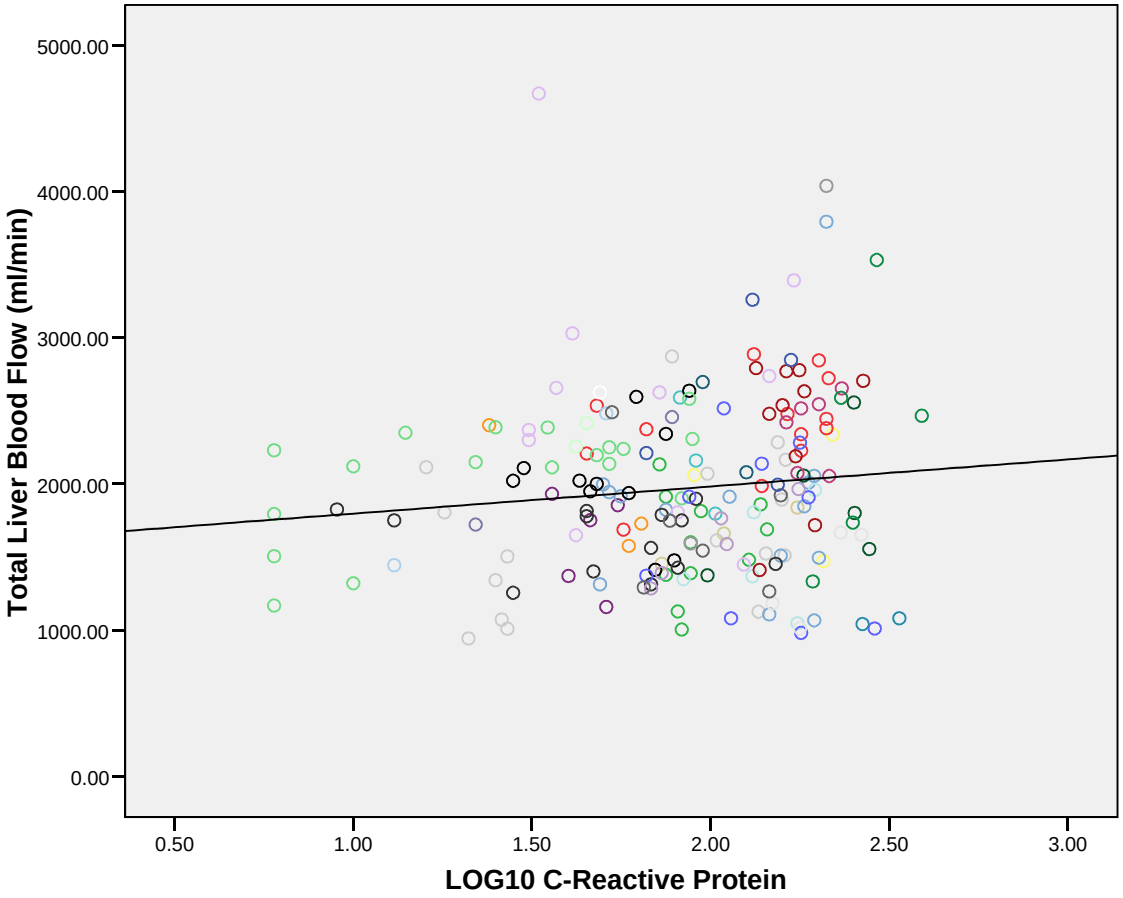

Figure 3 demonstrates portal venous blood flow in ml/min (y-axis) against C-Reactive Protein (x-axis) in all study patients. Individual patients are coded in different colours and the overall line of best fit is displayed.

Chapter 6 : Discussion and Conclusions

Advances in ultrasound technology have allowed measurement of individual arteries trans-abdominally and therefore non-invasively. This has mostly been applied in the oncological setting, where it is postulated that changes in blood flow are present when there are micrometastasis to the liver that are not detectable by other imaging. Most studies that have been carried out to assess liver blood flow in the setting of systemic inflammation have assessed total liver blood flow and have not assessed the individual contribution of the hepatic arterial and portal venous circulations. It is generally agreed across the literature that total liver blood flow is increased in systemic inflammation and the results of chapter 3 would corroborate this. It would also appear that increase in hepatic arterial flow is responsible for this and the portal venous flow is unchanged.

Since this study was performed there have been advances in techniques to measure blood flow and further studies should take advantage of these to minimise intra-observer error. Blood flow through the liver is difficult to measure in the clinical setting. In animals it is acceptable to cannulate the hepatic vein or place flow probes directly onto vessels operatively. In patients there are almost no clinical indications for hepatic venous cannulation and as this is an invasive procedure with morbidity attached, therefore it is unlikely that studies in critically ill patients measuring total liver blood flow by the Fick principal will be repeated. Magnetic Resonance Imaging (MRI) can provide the means of assessing liver perfusion however there are logistical difficulties of transferring ventilated patients to a MRI scanner where no metal is allowed in the room. This leaves us with ultrasound as a non-invasive method of assessment of portal venous and hepatic arterial blood flow. When trans-abdominal ultrasound was carried out there was found to be a variation of around 30% at 5

minute and 2 hour intervals where a stable mean arterial blood pressure was present. Endoscopic ultrasound allows almost direct contact with the portal vein and hepatic artery but justifying this in a study setting would be difficult.

Ultrasound contrast agents may help in assessing liver blood flow non-invasively. These small (typically 3 μm in diameter) gas filled bubbles are given intravenously and vibrate in the presence of an ultrasound signal, enhancing reflection. The recent developments in ultrasound contrast and software to interpret scans using this agent has allowed measurement of perfusion of the liver and may allow more accurate and repeatable measurement of portal venous and hepatic arterial flow. One advantage of this would be that the vessels themselves need not be imaged and a sonograph with an easily accessible area of liver could be re-imaged. This would make the scanning much easier and negate the effect of feed/gas in the duodenum which often leads to sub-optimal views of the vessels. The image would be recorded as the contrast bubbles perfused the liver and the computer software would generate perfusion graphs of the liver with a hepatic arterial and portal venous phase. Changes in intensity (or loudness) of a spectral Doppler signal are proportional to microbubble concentration.

The timing of liver blood flow changes has not been satisfactorily explained. Infusion of a pro-inflammatory cytokine in healthy volunteers provokes an increase in liver blood flow that occurs within 4 hours. The single study that has assessed liver blood flow using colour Doppler/duplex ultrasound in the intensive care setting had reported an increased hepatic arterial blood flow at 5 hours after the onset of illness, however this returned to normal after 24 hours. The question ‘What changes in hepatic arterial and portal venous flow occur at onset of inflammation and what are the timings of

these changes?' is not answered by these studies. Infusion of a pro-inflammatory cytokine in healthy volunteers is a very artificial situation and we have discussed in the introduction that, as well as pro-inflammatory cytokines, an appropriate hormonal environment is also necessary for the physiological changes of systemic inflammation to manifest themselves. Similarly the onset of systemic inflammation is very difficult to define and the study that measured hepatic arterial and portal venous flow 5 hours after admission to intensive care provides no information on how onset of systemic inflammation was derived. To assess the timing of changes in chapter 4 we chose an inflammatory stimulus that was repeatable and controlled. Classically the 'fight or flight' response, which is mediated by the adrenal medullary hormones, serves to divert blood away from the non-essential organs in favour of the heart, brain and kidneys.

Further work in this field is required to discover the mediator of changes in liver blood flow. It is understood that increased concentrations of metabolic products at a cellular level, elevated concentrations of circulating hormones and cytokines and increased cardiac output all cause increased liver blood flow and it is conceivable that any of these factors could be the cause of increased blood flow in systemic inflammation. Infusion of pro-inflammatory agents will stimulate the liver to produce acute phase proteins and glucose which will increase the concentration of metabolic products in the liver. Demonstration of an increase in liver blood flow in this situation will not indicate if blood flow is a direct effect of the pro-inflammatory cytokine or its effect on the liver. Hormones have been shown to have a direct effect on the splanchnic arterioles, exhibiting both alpha and beta adrenoceptor effects. An appropriate counter regulatory hormone environment will potentiate the effect of pro-

inflammatory cytokines on the liver and induce an acute phase response. Direct hormonal effects will be immediate and we would expect the effects of increased metabolism to be later. The acute phase proteins begin to appear at 6 hours post injury. Cortisol is increased maximally at 6 hours and white blood cells maximally at 8-10 hours. The peak concentration of C-Reactive protein is not seen until 48 hours. Our demonstration of increased hepatic arterial blood flow peaking at 4 hours post-operatively would not be supported by increased metabolic rate in the liver which goes on for at least 48 hours post injury. Nitric oxide is another potential mediator and while there is strong evidence in rats and mice that inhibition of nitric oxide synthase does not give the typical increase in liver blood flow seen after administration of lipopolysacharide or other inflammatory stimuli, this may not be simply extrapolated to humans. Nitric oxide and its effect on the liver have been studied in the cirrhotic liver and there is evidence that decreased nitric oxide is a factor in the increased vascular resistance and portal hypertension seen in cirrhotic liver disease. This has not been studied in critical illness. The changes that we have seen in the present study would more likely be hormonal or cytokine (or both) related and this study could be repeated with sampling of blood for assessment of these mediators.

The final study in the thesis demonstrated an increase in hepatic arterial flow and total liver blood flow in critically ill patients compared with controls. This concurs with previous studies and adds to the literature that these changes are mediated mainly by the hepatic artery. Serial blood flow measurements did not give any significant findings but there appeared to be a tendency to increased hepatic arterial flow with increased systemic inflammation.

We have shown that ultrasound assessment of hepatic arterial blood flow and portal venous blood flow can be carried out in the intensive care setting and that our results correspond to previously published work. The next step would be finding a clinical use for this test. The most likely use for this would be as a prognostic indicator. In the small numbers that we studies we were not able to show any differences in the survivors and non-survivors. An impression of serial results obtained was that the patients that survived had less variance in their blood flow with the corresponding level of systemic inflammation compared with those who died. A much larger study would be needed to statistically demonstrate such a relationship. It would also be useful to measure the changes in the components of liver blood flow before and after an intervention that is known to modulate the systemic inflammatory response and influence outcome (for example activated protein c). Further such investigations of the components of liver blood flow are required to understand better how the liver responds to inflammatory challenges and how such responses might influence survival.

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Appendices

Appendix 1 Chapter 3 patients

Table A
Control subjects

No	M0 F1	Age	TLBF	HAF	PVF	HATAM	PVTAM	HA XSA	PVXSA
1	1	57	1467	368	1098	19.8	16.2	0.31	1.13
2	0	77	1246	324	922	18.0	12.6	0.30	1.22
3	0	36	1391	322	1069	23.3	16.2	0.23	1.10
4	1	30	1715	333	1382	19.8	18.0	0.28	1.28
5	1	58	714	98	616	10.2	10.8	0.16	0.95
6	0	57	916	193	722	29.3	10.2	0.11	1.18
7	0	80	3141	569	2572	31.6	26.3	0.30	1.63
8	1	79	1831	302	1528	18.0	12.8	0.28	1.99
9	1	60	1103	233	869	14.4	9.0	0.27	1.61
10	0	77	1804	397	1406	18.4	12.6	0.36	1.86
11	0	58	1381	436	946	22.0	14.2	0.33	1.11
12	0	75	1911	572	1339	25.1	15.5	0.38	1.44
13	0	84	2050	363	1687	23.3	25.1	0.26	1.12
14	1	80	1700	391	1309	18.1	15.7	0.36	1.39
15	1	71	1957	556	1401	33.1	17.3	0.28	1.35
16	1	70	2309	689	1620	35.9	18.0	0.32	1.50
17	0	60	1892	458	1434	21.2	14.4	0.36	1.66
18	1	72	2503	403	2101	30.5	28.7	0.22	1.22

M Male F Female; TLBF Total liver blood flow (ml/min); HAF Hepatic artery flow volume (ml/min); PVF Portal venous flow volume (ml/min); HATAM Hepatic artery time-averaged velocity (cm/s); HAXSA Hepatic artery cross sectional area (cm^2); PVTAM Portal vein time-averaged velocity (cm/s); PVXSA Portal cross sectional area (cm^2).

Table B
Non-small cell lung cancers

No	M0 F1	Age	TLBF	HAF	PVF	HATAM	PVTAM	HA XSA	PVXSA
1	0	56	2904	730	2174	32.00	30.20	0.38	1.20
2	1	68	1786	467	1319	25.10	19.80	0.31	1.11
3	0	54	2068	677	1391	30.50	16.80	0.37	1.38
4	0	69	2031	680	1351	32.40	16.20	0.35	1.39
5	0	85	1769	379	1390	30.10	19.80	0.21	1.17
6	1	60	1812	650	1162	25.80	11.60	0.42	1.67
7	0	80	2939	1115	1824	41.30	18.20	0.45	1.67
8	0	69	969	295	674	20.50	10.90	0.24	1.03
9	0	79	1840	742	1097	39.90	15.50	0.31	1.18
10	0	49	1002	339	663	21.70	9.70	0.26	1.14

M Male F Female; TLBF Total liver blood flow (ml/min); HAF Hepatic artery flow volume (ml/min); PVF Portal venous flow volume (ml/min); HATAM Hepatic artery time-averaged velocity (cm/s); HAXSA Hepatic artery cross sectional area (cm^2); PVTAM Portal vein time-averaged velocity (cm/s); PVXSA Portal cross sectional area (cm^2).

Table C
Acute alcohol hepatitics

No	M0 F1	Age	TLBF	HAF	PVF	HATAM	PVTAM	HA XSA	PVXSA
1	0	46	1166	242	924	16.8	14.4	0.24	1.07
2	1	55	2595	1138	1457	47.4	13.2	0.40	1.84
3	0	50	2264	941	1323	54.1	13.2	0.29	1.67
4	0	51	1392	491	900	21.0	8.2	0.39	1.83
5	0	38	1093	405	688	30.7	9.8	0.22	1.17
6	0	45	2076	1050	1026	38.9	12.3	0.45	1.39
7	0	53	1470	738	732	29.3	8.3	0.42	1.47

M Male F Female; TLBF Total liver blood flow (ml/min); HAF Hepatic artery flow volume (ml/min); PVF Portal venous flow volume (ml/min); HATAM Hepatic artery time-averaged velocity (cm/s); HAXSA Hepatic artery cross sectional area (cm^2); PVTAM Portal vein time-averaged velocity (cm/s); PVXSA Portal cross sectional area (cm^2).

Appendix 2 Chapter 4 patients

Table A
Patients

Patient	M0 f1	Age	RA/OA	NSAID	Steroid	Immunosuppresor	Op Date	Joint
1	0	80	OA	No	no	No	09/07/2002	Knee
2	1	79	OA	ibuprofen	no	No	10/09/2002	Knee
3	1	63	RA	diclofenac	pred 3mg	sulphasalazine	10/09/2002	Hip
4	1	73	RA	naproxen	no	Gold	17/09/2002	Rev. knee
5	1	66	RA	No	no	No	17/09/2002	Knee
6	1	60	OA	vioxx	no	No	17/09/2002	Knee
7	0	77	OA	celebrex	no	No	17/09/2002	Knee
8	1	36	RA	celebrex	pred 7.5mg	Methotrexate	24/09/2002	Knee
9	0	76	OA	No	no	No	24/09/2002	Knee
10	0	75	OA	No	no	No	08/04/2003	Knee
11	0	58	OA	vioxx	no	No	08/04/2003	Knee
12	0	84	OA	No	no	No	15/04/2003	Hip
13	0	80	OA	No	no	No	29/04/2003	Rev. knee
14	1	71	OA	No	no	No	29/04/2003	Knee
15	1	63	OA	ibuprofen	no	No	10/06/2003	Knee
16	1	74	OA	No	no	No	10/06/2003	Knee
17	1	70	OA	naproxen	no	No	10/06/2003	Hip
18	0	60	OA	N	no	No	10/06/2003	Knee
19	1	72	OA	aspirin	no	No	29/07/2003	Knee
20	1	70	OA	No	no	No	29/07/2003	Knee

M male; F female; RA rheumatoid arthritis; OA osteoarthritis; NSAID non-steroidal anti-inflammatory drug

Table B
Blood flow measurements

Patient	Date	Time	HATAM	HAXSA	PVTAM	PVXSA	HAF	PVF	TLBF
1	08/07/2002	17:00	31.60	0.30	26.30	1.63	569	2572	3141
1	09/07/2002	12:30	23.00	0.31	7.60	1.49	428	679	1107
1	09/07/2002	14:30	29.90	0.33	10.50	1.72	592	1084	1676
1	09/07/2002	16:30	29.90	0.35	21.10	1.42	628	1798	2426
1	09/07/2002	18:30	23.30	0.30	16.10	1.57	419	1517	1936
1	10/07/2002	10:00	25.20	0.31	12.20	1.86	469	1362	1830
1	10/07/2002	17:00	21.60	0.28	12.40	1.48	363	1101	1464
1	11/07/2002	10:00	23.60	0.33	8.70	1.68	467	877	1344
2	09/09/2002	16:30	18.00	0.28	12.80	1.99	302	1528	1831
2	10/09/2002	16:00	34.40	0.27	14.40	1.63	557	1408	1966
2	10/09/2002	18:00	25.50	0.31	15.50	1.53	474	1423	1897
2	10/09/2002	20:00	21.50	0.30	12.60	1.64	387	1240	1627
2	10/09/2002	22:00	19.80	0.34	10.80	1.57	404	1017	1421
2	11/09/2002	09:00	21.50	0.27	16.60	1.43	348	1424	1773
2	11/09/2002	18:00	19.80	0.28	8.70	1.67	333	872	1204
3	09/09/2002	16:45	36.10	0.22	16.60	1.44	477	1434	1911
3	10/09/2002	12:20	26.50	0.29	12.00	1.36	461	979	1440
3	10/09/2002	14:20	36.10	0.29	15.00	1.39	628	1251	1879
3	10/09/2002	16:20	42.80	0.35	15.00	1.31	899	1179	2078
3	10/09/2002	18:20	42.10	0.33	24.10	1.35	834	1952	2786
3	11/09/2002	09:15	32.20	0.29	16.40	1.48	560	1456	2017
3	11/09/2002	18:00	21.50	0.29	23.30	1.39	374	1943	2317
4	16/09/2002	15:45	21.50	0.28	14.40	1.79	361	1547	1908
4	17/09/2002	12:00	16.70	0.35	15.00	1.57	351	1413	1764
4	17/09/2002	14:00	26.90	0.39	18.00	1.23	629	1328	1958
4	17/09/2002	16:00	36.10	0.33	23.30	1.19	715	1664	2378
4	17/09/2002	18:00	16.20	0.28	18.00	1.47	272	1588	1860
4	18/09/2002	10:00	28.70	0.40	16.20	1.79	689	1740	2429
4	18/09/2002	18:00	16.20	0.34	23.30	1.31	330	1831	2162
5	16/09/2002	16:00	19.80	0.27	16.20	1.80	321	1750	2070
5	17/09/2002	17:00	14.40	0.38	14.40	1.40	328	1210	1538
5	17/09/2002	19:00	23.30	0.37	12.60	1.43	517	1081	1598
5	17/09/2002	21:00	23.30	0.33	12.60	1.65	461	1247	1709
5	18/09/2002	10:00	18.00	0.36	12.60	1.66	389	1255	1644
5	18/09/2002	18:00	23.30	0.33	18.00	1.68	461	1814	2276
6	16/09/2002	16:10	14.40	0.27	9.00	1.61	233	869	1103
6	17/09/2002	11:45	12.60	0.36	9.00	1.45	272	783	1055
6	17/09/2002	13:45	19.80	0.31	10.80	1.56	368	1011	1379
6	17/09/2002	15:45	35.90	0.34	7.20	1.28	732	553	1285
6	17/09/2002	17:45	18.00	0.31	14.40	1.38	335	1192	1527
6	18/09/2002	10:00	16.20	0.26	10.80	1.25	253	810	1063
6	18/09/2002	18:00	14.40	0.30	12.60	1.70	259	1285	1544
7	16/09/2002	16:30	18.40	0.36	12.60	1.86	397	1406	1804
7	17/09/2002	15:30	12.50	0.35	5.20	1.60	263	499	762
7	17/09/2002	17:30	12.50	0.35	7.20	1.64	263	708	971
7	17/09/2002	19:30	16.40	0.28	10.40	1.52	276	948	1224
7	17/09/2002	21:30	14.40	0.30	9.00	1.50	259	810	1069
7	18/09/2002	10:00	18.00	0.30	9.00	1.58	324	853	1177
7	18/09/2002	18:00	34.10	0.35	16.20	1.90	716	1847	2563
8	23/09/2002	16:00	23.60	0.26	14.40	1.47	368	1270	1638

8	24/09/2002	16:30	25.10	0.27	9.00	1.58	407	853	1260
8	24/09/2002	18:30	21.50	0.30	9.00	1.38	387	745	1132
8	24/09/2002	20:30	23.30	0.30	10.80	1.58	419	1024	1443
8	24/09/2002	22:30	18.00	0.32	10.30	1.54	346	952	1297
8	25/09/2002	10:00	21.50	0.29	16.60	1.65	374	1643	2018
8	25/09/2002	18:00	19.80	0.29	14.40	1.75	345	1512	1857
9	23/09/2002	16:00	18.00	0.27	12.60	1.24	292	937	1229
9	24/09/2002	confused							
10	07/04/2003	15:45	25.10	0.38	15.50	1.44	572	1339	1911
10	08/04/2002	11:00	30.50	0.35	16.20	1.26	641	1225	1865
10	08/04/2002	13:00	19.80	0.39	16.20	1.33	463	1293	1756
10	08/04/2002	15:00	18.00	0.35	12.60	1.31	378	990	1368
10	08/04/2002	17:00	20.40	0.36	18.00	1.34	441	1447	1888
10	09/04/2002	09:00	25.10	0.36	18.00	1.40	542	1512	2054
10	09/04/2003	18:00	25.10	0.39	18.70	1.38	587	1548	2136
11	07/04/2003	16:00	22.00	0.33	14.20	1.11	436	946	1381
11	08/04/2002	arrest							
12	14/04/2003	16:00	23.30	0.26	25.10	1.12	363	1687	2050
12	15/04/2003	16:00	25.10	0.30	16.30	1.23	452	1203	1655
13	28/04/2003	16:00	18.10	0.36	15.70	1.39	391	1309	1700
14	28/04/2003	16:00	33.10	0.28	17.30	1.35	556	1401	1957
14	29/04/2003	11:00	35.90	0.25	15.50	1.34	539	1246	1785
14	29/04/2003	13:00	32.30	0.25	18.00	1.41	485	1523	2007
14	29/04/2003	15:00	38.90	0.30	14.40	1.34	700	1153	1854
14	29/04/2003	17:00	21.50	0.30	15.50	1.40	387	1302	1689
14	30/04/2003	10:00	26.70	0.32	12.00	1.33	513	958	1470
14	30/04/2003	17:00	30.30	0.30	14.40	1.35	545	1166	1712
15	09/06/2003	18:00	20.10	0.35	16.20	1.19	422	1157	1579
15	10/06/2003	11:00	23.30	0.33	16.60	1.15	461	1145	1607
16	09/06/2003	18:00	26.90	0.33	16.20	1.20	533	1166	1699
16	10/06/2003	13:00	30.90	0.34	12.60	1.28	630	968	1598
17	09/06/2003	18:00	35.90	0.32	18.00	1.50	689	1620	2309
17	10/06/2003	11:00	21.10	0.34	5.20	1.45	430	452	883
17	11/06/2003	13:00	23.30	0.34	12.20	1.48	475	1083	1559
18	09/06/2003	18:00	21.20	0.36	14.40	1.66	458	1434	1892
18	10/06/2003	13:00	18.00	0.40	9.20	1.59	432	878	1310
18	10/06/2003	15:00	24.40	0.37	12.60	1.60	542	1210	1751
19	28/07/2003	16:00	30.50	0.22	28.70	1.22	403	2101	2503
19	29/07/2003	11:00	27.70	0.25	19.80	1.15	416	1366	1782
19	29/07/2003	13:00	25.10	0.24	18.00	1.16	361	1253	1614
19	29/07/2003	15:00	30.90	0.25	18.00	1.20	464	1296	1760
19	29/07/2003	17:00	31.80	0.24	17.10	1.19	458	1221	1679
19	30/07/2003	10:00	32.00	0.24	24.60	1.20	461	1771	2232
20	28/07/2003	16:00	25.40	0.41	28.10	1.66	625	2799	3424
20	29/07/2003	13:00	22.20	0.38	9.80	1.47	506	864	1371
20	29/07/2003	15:00	27.80	0.40	18.00	1.44	667	1555	2222
20	29/07/2003	17:00	26.60	0.40	25.10	1.45	638	2184	2822
20	29/07/2003	19:00	22.20	0.39	19.90	1.49	519	1779	2299
20	30/07/2003	11:00	28.00	0.38	17.40	1.50	638	1566	2204

TLBF Total liver blood flow (ml/min); HAF Hepatic artery flow volume (ml/min); PVF Portal venous flow volume (ml/min); HATAM Hepatic artery time-averaged velocity (cm/s); HAXSA Hepatic artery cross sectional area (cm^2); PVTAM Portal vein time-averaged velocity (cm/s); PVXSA Portal cross sectional area (cm^2).

Appendix 3 Chapter 5 patients

Patient	1
Age	29 years
Sex	Female
Reason for admission	post op, abdomen
APACHE II	10
Predicted mortality	3.3%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
1	0	16/11/2001	66			1087	1127	2214						
1	1	17/11/2001	131			774	2484	3261						

Patient	2
Age	78 years
Sex	Male
Reason for admission	post op, abdomen
APACHE II	28
Predicted mortality	77.5%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
2	0	17/11/2001	71	12	8				y		y	y		
2	1	18/11/2001	59	9	11				y		y	y		
2	2	19/11/2001	110	13	15	543	587	1130	y		y		y	
2	3	20/11/2001	81	11	10	479	900	1379	y		y			
2	4	21/11/2001	75	8	12	227	777	1004	y		y		y	
2	5	22/11/2001	83	8	14	421	1062	1483	y		y		y	
2	6	23/11/2001	128	12	15	871	821	1692	y		y		y	
2	7	24/11/2001	144	14	14	875	986	1861	y		y		y	
2	8	25/11/2001	138	16	12	605	1213	1814	y		y			
2	9	26/11/2001	94	15	10	454	1148	1602	y		y			
2	10	27/11/2001	88	17	10	810	1328	2134	y		y			
2	11	28/11/2001	72	18		468	925	1389	y		y			
2	12	29/11/2001	88	19		745	1170	1915	y		y			
2	13	30/11/2001	75	18					y		y			
2	14	01/12/2001	59		7				y		y			
2	15	02/12/2001	54		6				y		y			
2	16	03/12/2001	62	20	12				y		y		y	
2	17	04/12/2001	153		13				y		y		y	
2	18	05/12/2001	188	23	10				y		y		y	
2	19	06/12/2001	158						y		y		y	

Patient	3
Age	53 years
Sex	Male
Reason for admission	post op, abdomen
APACHE II	11
Predicted mortality	5.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
3	0	04/12/2001	73			378	1076	1454						
3	1	05/12/2001	109			454	1209	1663						
3	2	06/12/2001												
3	3	07/12/2001												
3	4	08/12/2001	175			500	1339	1839						

Patient	4
Age	73 years
Sex	Female
Reason for admission	post op, vascular
APACHE II	15
Predicted mortality	21.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
4	0	01/02/2002	151	22	9.5				y		y			
4	1	02/02/2002	159		5.1				y		y			
4	2	03/02/2002	177	18	7.4				y		y			
4	3	04/02/2002	149	19	6.2				y		y			
4	4	05/02/2002	112	21	6.3				y		y			
4	5	06/02/2002	91	23	8.8				y		y			
4	6	07/02/2002	75	22	10.9				y		y			
4	7	08/02/2002	53	22	11.9				y		y			
4	8	09/02/2002	47	22	14.4				y		y			
4	9	10/02/2002	52	24	12.8				y		y			
4	10	11/02/2002	36	22	11.6				y		y			
4	11	12/02/2002	58	42	10.2				y		y			
4	12	13/02/2002	84	25	9				y		y			
4	13	14/02/2002	80	26	10.4				y		y			
4	14	15/02/2002	53		9.1	292	867	1159	y		y			
4	15	16/02/2002	51	25	7.3	392	1361	1753	y		y			
4	16	17/02/2002	46		7	335	1037	1371	y		y			
4	17	18/02/2002	40	27	7.5	378	1555	1933	y		y			
4	18	19/02/2002	36		6.9	356	1501	1857						
4	19	20/02/2002	55	29	10.1									

Patient	5
Age	65 years
Sex	Male
Reason for admission	post op, vascular
APACHE II	13
Predicted mortality	5.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
5	0	16/2/2002	90	27	8.8	378	1684	2062						
5	1	17/2/2002	207	27	11.1	558	914	1472						
5	2	18/2/2002	220	26	9.5	605	1735	2340						

Patient	6
Age	69 years
Sex	Male
Reason for admission	post op, plastic surgery
APACHE II	16
Predicted mortality	11.2%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
6	0	13/12/2001	208	26	14.9					y				
6	1	14/12/2001	166	20	11					y	y			
6	2	15/12/2001	188		12.3					y	y			
6	3	16/12/2001	196		14	756	1724	2480		y	y			
6	4	17/12/2001	164	18	11.1	813	1908	2725		y	y			
6	5	18/12/2001	214		13.2	903	2113	3016		y	y			
6	6	19/12/2001		22	16.1	587	1792	2383		y	y			
6	7	20/12/2001	211	19	17.5					y	y			
6	8	21/12/2001	199	17	17					y	y		y	
6	9	22/12/2001	230	15	18					y	y		y	
6	10	23/12/2001	243		18.7	292	2152	2444		y	y		y	
6	11	24/12/2001	211	18	14.6					y	y		y	
6	12	25/12/2001	197		13.1					y	y		y	
6	13	26/12/2001	203	20	10.9					y	y		y	
6	14	27/12/2001	224		16.2	511	2332	2847		y	y			
6	15	28/12/2001	201	23	20.6					y	y			
6	16	29/12/2001	198		14.5					y	y			
6	17	30/12/2001	169		13.7	511	2376	2887		y	y			
6	18	31/12/2001	132	19	13.9	396	1591	1987		y	y			
6	19	01/01/2002	139	21	16.6					y	y			
6	20	02/01/2002	180	19	18.5	454	1890	2340		y	y			

6	21	03/01/2002	179		19.5	421	1807	2228		y	y			
6	22	04/01/2002	162	18	17.5					y	y			
6	23	05/01/2002	142	18	16.5					y	y			
6	24	06/01/2002	124		16					y	y			
6	25	07/01/2002	104	19	17					y	y			
6	26	08/01/2002	81		16.5					y	y			
6	27	09/01/2002	83	20	19					y	y			
6	28	10/01/2002	94	21	14.8					y	y			
6	29	11/01/2002	69	24	13.8					y	y			
6	30	12/01/2002	60		13.4					y	y			
6	31	13/01/2002	50	24	15.2					y	y			
6	32	14/01/2002	45	23	13.7	392	1818	2210		y	y			
6	33	15/01/2002	66		13.7	270	2106	2376		y	y			
6	34	16/01/2002	48	24	11.3	450	2084	2534		y	y			
6	35	17/01/2002	57		14.5	263	1425	1688		y				

Patient	7
Age	64 years
Sex	Male
Reason for admission	post op, vascular
APACHE II	28
Predicted mortality	78.6%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
7	0	16/02/2002							y		y		y	y
7	1	17/02/2002	171	19	30.8				y		y		y	y
7	2	18/02/2002	139	19	26.9	623	1177	1800	y		y			y
7	3	19/02/2002	103		25.7	763	1828	2591	y		y			y
7	4	20/02/2002	82	20	27.7	745	1415	2160	y		y			y
7	5	21/02/2002		20	27.1				y		y			y
7	6	22/02/2002	91	20	26.5				y		y			y
7	7	23/02/2002	107	20	26.7				y		y			y
7	8	24/02/2002	154	22	32.3				y		y			y
7	9	25/02/2002	163	19	30.4				y		y			y
7	10	26/02/2002	192	18	25.2				y		y			y
7	11	27/02/2002	196	20	22.5				y		y			y
7	12	28/02/2002	149	20	31.3				y		y		y	y
7	13	01/03/2002	140	17	36.9				y		y			y
7	14	02/03/2002		21	39.1				y		y		y	y
7	15	03/03/2002		17	56.6				y		y		y	y

Patient	8
Age	77 years
Sex	Male
Reason for admission	medical
APACHE II	31
Predicted mortality	73.3%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
8	0	28/02/2002	69	18	9.4				y		y			
8	1	01/03/2002	162	17	10.7				y		y			
8	2	02/03/2002	195	19	13.8				y		y		y	y
8	3	03/03/2002	168	19	13.6				y		y		y	y
8	4	04/03/2002	112	18	11.7				y		y		y	y
8	5	05/03/2002	97	19	13.3				y		y			y
8	6	06/03/2002	74	19	10.4				y		y			y
8	7	07/03/2002	83	19					y		y			y
8	8	08/03/2002	95	18	9.4				y		y		y	y
8	9	09/03/2002	94	17	9.3				y		y		y	y
8	10	10/03/2002		19					y		y			
8	11	11/03/2002	122	21	9.6				y		y			
8	12	12/03/2002	133		8.2				y		y			
8	13	13/03/2002	105	19	6.8				y		y			
8	14	14/03/2002	95	21	8.8				y		y			
8	15	15/03/2002	107	21					y		y			
8	16	16/03/2002	135	21	13.9				y		y			
8	17	17/03/2002	159		10.1				y		y			
8	18	18/03/2002	171	20	13.6				y		y		y	
8	19	19/03/2002	154		15.5	641	1645	2286	y		y			
8	20		162			576	1591	2167						

8	20.5	20/03/2002	158	19		407	1487	1893	y		y			y
8	21		161			248	1263	1512						
8	21.5	21/03/2002	143	20	22.9	450	1076	1526	y		y			y
8	22		136			281	846	1127						
8	22.5	22/03/2002	104	21	19.4	248	1368	1616	y		y		y	y
8	23	23/03/2002	95	20	12.6				y		y		y	y
8	24	24/03/2002	46	20	11				y		y			y
8	25	25/03/2002	27	23		176	835	1011	y		y			y
8	26		21			184	759	943						
8	26.5	26/03/2002	18	25	20.7	353	1451	1807	y		y			y
8	27		16			507	1609	2116						
8	27.5	27/03/2002	25	24	24.2	443	900	1343	y		y			y
8	28		26			187	885	1073						
8	28.5	28/03/2002	27	28	31.3	295	1206	1504	y		y			y
8	29	29/03/2002	15	26	30.9				y		y			y
8	30	30/03/2002	8	25	28.6				y		y			y
8	31	31/03/2002	6	24	31.3				y		y			y
8	32	01/04/2002	6	25					y		y			
8	33	02/04/2002	19	23	15.9				y		y		y	
8	34	03/04/2002	12	24	24.3				y		y			
8	35	04/04/2002	19		28.9					y	y			
8	36	05/04/2002	122	24						y	y			
8	37	06/04/2002	135	25	22.8					y	y		y	
8	38	07/04/2002	92		20.9					y	y			
8	39	08/04/2002	97	24						y	y		y	
8	40	09/04/2002	98			561	1508	2070		y	y			
8	41	10/04/2002	95	22						y	y			
8	42	11/04/2002	78			968	1904	2872		y	y			
8	43	12/04/2002	73	27						y	y			

Patient	9
Age	46 years
Sex	Male
Reason for admission	burns
APACHE II	7
Predicted mortality	3.3%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
9	0	14/03/2002							y		y			
9	1	15/03/2002	16	26	8.6				y		y			
9	2	16/03/2002	137	19	9.6				y		y			
9	3	17/03/2002	181	18	7.2				y		y			
9	4	18/03/2002	210	20	6.3				y		y			
9	5	19/03/2002	211		8.2	1299	2494	3794	y		y			
9	6	20/03/2002	195	19	7.8	673	1382	2055	y		y			
9	6.5		201			828	666	1494						
9	7	21/03/2002	183		14.7	1141	705	1850	y		y			
9	7.5		188			392	1616	2012						
9	8	22/03/2002	195	22	14.4	378	691	1069	y		y			
9	9	23/03/2002	136	21	13.2				y		y			
9	10	24/03/2002	140	23	17.6				y		y			
9	11	25/03/2002	157		18.2	461	1047	1508	y		y			
	11.5		146			403	705	1109						
9	12	26/03/2002	113	26	13.2	540	1375	1911	y		y			
9	12.5		75			918	907	1825						
9	13	27/03/2002	56	26	11.6	579	1335	1915	y		y			
9	13.5		49			392	921	1314						
9	14	28/03/2002	50	27	10.3	597	1400	1998	y		y			

9	14.5		52			490	1454	1944						
9	15	29/03/2002	69	26	10.1				y		y			
9	16	30/03/2002	72	27	9.4				y		y			

Patient	10
Age	70 years
Sex	Female
Reason for admission	post op, vascular
APACHE II	21
Predicted mortality	23.8%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
10	0	01/04/2002	8	20					y		y			
10	1	02/04/2002	22	23	6	565	810	1375	y		y			
10	2	03/04/2002	182	24	16	810	1249	2059	y		y			
10	2.5		252			817	1742	2555						
10	3	04/04/2002	253		18	680	1123	1803	y		y			
10	3.5		278			648	907	1555						

Patient	11
Age	31 years
Sex	Female
Reason for admission	post op, plastics
APACHE II	14
Predicted mortality	26.8%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
11	0	21/04/2002			7				y		y		y	
11	1	22/04/2002	95	15	5				y		y		y	
11	2	23/04/2002	68	15	7	623	1105	1728	y		y			
11	3	24/04/2002	59	16	7	655	921	1576	y		y			
11	4	25/04/2002	47	18	7	925	1954	2879	y		y			
11	5	26/04/2002	24	19	5	608	1792	2401						

Patient	12
Age	49 years
Sex	Female
Reason for admission	medical
APACHE II	13
Predicted mortality	16.5%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
12	0	21/04/2002	116	22	6.4				y		y			
12	1	22/04/2002	162	23	7.5				y		y			
12	2	23/04/2002	171	21	9.4	803	2588	3391	y		y			
	2.5	23/04/2002	146			759	1980	2739						
12	3	24/04/2002	124	17	8.4	407	1040	1447	y		y			
12	4	25/04/2002	81	14	10.5	529	1281	1807	y		y			
12	5	26/04/2002	72	15	13.5	767	1857	2627	y		y			
12	6	27/04/2002	49	18	21.4				y		y			
12	7	28/04/2002	52	19	19.6				y		y			
12	8	29/04/2002	42	20	18.8	623	1029	1648	y		y			
	8.5	29/04/2002	37			903	1753	2656						
12	9	30/04/2002	33	19	16.4	1159	3509	4668	y		y			
	9.5	30/04/2003	31			792	1576	2368						
12	10	01/05/2002	30	21	15.3				y		y			
12	11	02/05/2002	31	21	12.4	813	1487	2300	y		y			
12	12	03/05/2002	41	22	12.5	936	2095	3031	y		y			
12	13	04/05/2002	56	24	11.9				y		y			
12	14	05/05/2002	53	24	8.8				y		y			
12	15	06/05/2002	62	27	10.4				y		y			
12	16	07/05/2002	74	27	13.5				y		y			
12	17	08/05/2002	100	29	10.9				y		y			

12	18	09/05/2002	87	29	10.5									

Patient	13
Age	77 years
Sex	Male
Reason for admission	post op, vascular
APACHE II	21
Predicted mortality	38.9%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
13	0	07/06/2002							y		y			
13	1	08/06/2002		25					y		y			
13	2	09/06/2002	144	24	16				y		y			
13	3	10/06/2002	126	24	17	680	1400	2080	y		y			
13	4	11/06/2002	107	24	19	824	1753	2577	y		y			
13	5	12/06/2002	103	25	16				y		y			
13	6	13/06/2002	95		15	1015	1684	2699	y		y			

Patient	14
Age	21 years
Sex	Male
Reason for admission	post op, plastics
APACHE II	10
Predicted mortality	5.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
14	0	11/06/2002	18	33	25.5				y		y			
14	1	12/06/2002	50	33	21				y		y			
14	2	13/06/2002	45	29	16.2	1433	986	2415	y		y			
14	3	14/06/2002	16	26	11.1									
14	4	15/06/2002	42	34	11.9	803	1454	2257						

Patient	15
Age	75 years
Sex	Female
Reason for admission	pancreatitis
APACHE II	26
Predicted mortality	50.7%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
15	0	19/06/2002	163	22	15.3	324	2098	2422	y		y			
15	1	20/06/2002	224	21	14.6	407	1648	2055	y		y		y	y
15	2	21/06/2002	179	17	16.1	547	1972	2519	y		y		y	y
15	3	22/06/2002	174	16	15.7				y		y		y	y
15	4	23/06/2002	174	18	25.4				y		y		y	y
15	5	24/06/2002	201	18	28.4	853	1692	2545	y		y		y	y
15	6	25/06/2002	191	21	31.4				y		y		y	y
15	7	26/06/2002			23.3				y		y		y	y
15	8	27/06/2002	175		32.1	601	1472	2073	y		y		y	y
15	9	28/06/2002	175	22	22.8	615	1386	2001	y		y		y	y
15	10	29/06/2002	179	22	21				y		y		y	y
15	11	30/06/2002	229	22	20.1				y		y		y	y
15	12	01/07/2002	218	22	17.2	659	1998	2653	y		y		y	y
15	13	02/07/2002	233	19	29.3				y		y		y	y

Patient	16
Age	66 years
Sex	Female
Reason for admission	medical
APACHE II	30
Predicted mortality	49.3%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
16	0	23/06/2002		22	12				y		y			
16	1	24/06/2002	211	26	18	1472	2566	4038	y		y			
16	2	25/06/2002			27				y		y			
16	3	26/06/2002	83	26		666	929	1594	y		y	y		

Patient	17
Age	37 years
Sex	Male
Reason for admission	post op, abdomen
APACHE II	19
Predicted mortality	48.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
17	0	27/06/2002	258	32	24				y		y			
17	1	28/06/2002	208	26	18				y		y			
17	2	29/06/2002	193	21	13				y		y			
17	3	30/06/2002	197	23	15				y		y			
17	4	01/07/2002	142	23	15				y		y			
17	5	02/07/2002	119	24	19				y		y			
17	6	03/07/2002	87	22	18	328	2311	2638	y		y			
17	7	04/07/2002	90	25	16		1195		y		y			
17	8	05/07/2002	79	26	17				y		y			
17	9	06/07/2002	71	26	14				y		y			
17	10	07/07/2002	63		14				y		y			
17	11	08/07/2002	70	29	16	317	1094	1415	y		y			
17	12	09/07/2002	62	29	14	738	1857	2595	y		y			
17	13	10/07/2002	59	34	20	587	1350	1936	y		y			
17	14	11/07/2002	43	32	18	648	1375	2023	y		y			
17	15	12/07/2002	79	32	14	648	831	1479	y		y			
17	16	13/07/2002	136	33	14				y		y			
17	17	14/07/2002	174	32	15				y		y			
17	18	15/07/2002	248	35	19				y		y			
17	19	16/07/2002	139	30	12				y		y			
17	20	17/07/2002		23	11				y		y			

17	21	18/07/2002	85	32	11				y		y			
17	22	19/07/2002	68	33	12				y		y			
17	23	20/07/2002	53	33	12				y		y			
17	24	21/07/2002	43	34	13				y		y			
17	25	22/07/2002	28	33	11	533	1487	2023	y		y			
17	26	23/07/2002	30	35	20	529	1580	2109	y		y			
17	27	24/07/2002	75	31	18	745	1598	2343	y		y			
17	28	25/07/2002	48	32	19	507	1494	2001	y		y			
17	29	26/07/2002	46	34	19	543	1407	1951	y		y			
17	30	27/07/2002	62	35	20				y		y			
17	31	28/07/2002	45	35	20				y		y			
17	32	29/07/2002	31	37	21									
17	33	30/07/2002												

Patient	18
Age	55 years
Sex	Female
Reason for admission	post op, abdomen
APACHE II	18
Predicted mortality	28.9%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
18	0	08/07/2002	84	16	22	551	799	1350	y		y			
18	1	09/07/2002	196	18	27	943	1019	1958	y		y			
18	2	10/07/2002	175	20	17	400	651	1047	y		y			
18	3	11/07/2002	132	18	11	619	1188	1807	y		y		y	
18	4	12/07/2002	131	20	10	493	875	1368	y		y		y	
18	5	13/07/2002	130	20	8				y		y			
18	6	14/07/2002	133	22	16				y		y			
18	7	15/07/2002	174	20	14				y		y			
18	8	16/07/2002	85	21	10				y		y			
18	9	17/07/2002	51	22	10				y		y			

Patient	19
Age	67 years
Sex	Male
Reason for admission	post op, neurosurgery
APACHE II	26
Predicted mortality	35.2%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
19	0	15/08/2002	50	23					y		y			
19	1	16/08/2002	88	24					y		y			
19	2	17/08/2002	103	22					y		y			
19	3	18/08/2002	64	23					y		y			
19	4	19/08/2002	49	25		468	2160	2627		y	y			
19	5	20/08/2002	72	26			2307			y	y			
19	6	21/08/2002	141	26						y	y			

Patient	20
Age	65 years
Sex	Female
Reason for admission	medical
APACHE II	25
Predicted mortality	62.9%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
20	0	13/08/2002	22	30	17	281	1440	1724	y		y			
20	1	14/08/2002	78	35	13	407	2052	2458	y		y			

Patient	21
Age	84 years
Sex	Male
Reason for admission	post op, vascular
APACHE II	21
Predicted mortality	57.0%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
21	0	13/08/2002							y		y			
21	1	14/08/2002							y		y		y	
21	2	15/08/2002							y		y		y	
21	3	16/08/2002							y		y			
21	4	17/08/2002							y		y			
21	5	18/08/2002							y		y			
21	6	19/08/2002	57			510	1731	2242	y		y			
21	7	20/08/2002	52			605	1647	2253	y		y			
21	8	21/08/2002	48			661	1537	2199	y		y			
21	9	22/08/2002	35			560	1827	2386	y		y			
21	10	23/08/2002							y		y			
21	11	24/08/2002							y		y			
21	12	25/08/2002							y		y			
21	13	26/08/2002							y		y			
21	14	27/08/2002							y		y			
21	15	28/08/2002							y		y			
21	16	29/08/2002	89			815	1494	2307	y		y			
21	17	30/08/2002	83			430	1472	1900	y		y			
21	18	31/08/2002							y		y			
21	19	01/09/2002							y		y			
21	20	02/09/2002	87			446	2137	2584	y		y			

21	21	03/09/2002	52			462	1676	2138	y		y			
21	21	04/09/2002	36			542	1572	2113	y		y			
21	22	05/09/2002	25			530	1858	2390	y		y			
21	23	06/09/2002	22			602	1548	2149	y		y			
21	24	07/09/2002							y		y			
21	25	08/09/2002							y		y			
21	26	09/09/2002	14			461	1890	2350	y		y			
21	27	10/09/2002	10			419	1702	2120	y		y			
21	28	11/09/2002	10			285	1037	1321	y		y			
21	29	12/09/2002							y		y			
21	30	13/09/2002							y		y			
21	31	14/09/2002							y		y			
21	32	15/09/2002							y		y			
21	33	16/09/2002	6			310	858	1170	y		y			
21	34	17/09/2002	6			335	1460	1796	y		y			
21	35	18/09/2002	6			546	1684	2232	y		y			
21	36	19/09/2002	6			482	1024	1504	y		y			
21	37	20/09/2002												

Patient	22
Age	64 years
Sex	Male
Reason for admission	post op, thoracic
APACHE II	20
Predicted mortality	30.0%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
22	0	09/11/2002							y		y			
22	1	10/11/2002							y		y			
22	2	11/11/2002							y		y			
22	3	12/11/2002	152			391	1063	1454	y		y			
22	4	13/11/2002	91			455	1444	1897	y		y			
22	5	14/11/2002	81			497	930	1425	y		y			
22	6	15/11/2002	68			346	967	1314	y		y			
22	7	16/11/2002	47			297	1106	1404	y		y			
22	8	17/11/2002	28			239	1017	1256	y		y			
22	9	18/11/2002	83			315	1436	1749	y		y			
22	10	19/11/2002	68			371	1192	1562	y		y			
22	11	20/11/2002	45			333	1447	1778	y		y			
22	12	21/11/2002	73			325	1462	1789	y		y			
22	13	22/11/2002	45			395	1421	1814	y		y			
22	14	23/11/2002							y		y			
22	15	24/11/2002							y		y			
22	16	25/11/2002							y		y			
22	17	26/11/2002							y		y			
22	18	27/11/2002	13			346	1406	1753	y		y			
22	19	28/11/2002							y		y			
22	20	29/11/2002	9			316	1510	1825	y		y			

22	21	30/11/2002							y		y			
22	22	01/12/2002							y		y			
22	23	02/12/2002								y	y			
22	24	03/12/2002								y	y			
22	25	04/12/2002								y	y			
22	26	05/12/2002								y	y			
22	27	06/12/2002								y	y			
22	28	07/12/2002								y	y			
22	29	08/12/2002								y	y			
22	30	09/12/2002								y	y			
22	31	10/12/2002								y	y			
22	32	11/12/2002								y	y			
22	33	12/12/2002								y	y			

Patient	23
Age	43 years
Sex	Male
Reason for admission	post op, plastics
APACHE II	27
Predicted mortality	38.6%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
23	0	17/11/2002							y		y			y
23	1	18/11/2002							y		y			Y
23	2	19/11/2002							y		y			Y
23	3	20/11/2002							y		y			Y
23	4	21/11/2002							y		y			Y
23	5	22/11/2002	51			738	1746	2484	y		y			Y
23	6	23/11/2002							y		y			Y
23	7	24/11/2002							y		y			Y
23	8	25/11/2002							y		y			
23	9	26/11/2002							y		y			
23	10	27/11/2002	13			533	913	1443	y		y			
23	11	28/11/2002							y		y			
23	12	29/11/2002							y		y			
23	13	30/11/2002							y		y			
23	14	01/12/2002							y		y			
23	15	02/12/2002							y		y			
23	16	03/12/2002							y		y			
23	17	04/12/2002							y		y			
23	18	05/12/2002							y		y			
23	19	06/12/2002							y		y			
23	20	07/12/2002							y		y			

23	21	08/12/2002							y		y			
23	22	09/12/2002							y		y			
23	23	10/12/2002							y		y			
23	24	11/12/2002							y		y			
23	25	12/12/2002							y		y			
23	26	13/12/2002							y		y			
23	27	14/12/2002							y		y			
23	28	15/12/2002							y		y			
23	29	16/12/2002							y		y			
23	30	17/12/2002							y		y			
23	31	18/12/2002												
23	32	19/12/2002												

Patient	24
Age	29 years
Sex	Male
Reason for admission	pancreatitis
APACHE II	26
Predicted mortality	68.6%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
24	0	12/01/2003							y		y			Y
24	1	13/01/2003	267			1144	1562	2707	y		y			
24	2	14/01/2003	196			509	1209	1717	y		y			
24	3	15/01/2003	146			620	1860	2480	y		y			
24	4	16/01/2003	134			1219	1574	2793						
24	5	17/01/2003	163			997	1775	2771						
24	6	18/01/2003	173			732	1457	2188						
24	7	19/01/2003	183			943	1691	2635						
24	8	20/01/2003	177			821	1958	2779						
24	9	21/01/2003	159			806	1733	2537						
24	10	22/01/2003	137			693	718	1411						

Patient	25
Age	38 years
Sex	Female
Reason for admission	post op, abdomen
APACHE II	14
Predicted mortality	30.8%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
25	0	16/01/2003							y		y		y	
25	1	17/01/2003							y		y	y	y	
25	2	18/01/2003							y		y	y	y	
25	3	19/01/2003	288			371	644	1011	y		y	y	y	
25	4	20/01/2003	179			324	659	983	y		y			
25	5	21/01/2003	114			234	849	1083	y		y	y		
25	6	22/01/2003	66			338	1033	1371	y		y			
25	7	23/01/2003							y		y			
25	8	24/01/2003	178			561	1724	2282	y		y			
25	9	25/01/2003							y		y			
25	10	26/01/2003							y		y			
25	11	27/01/2003	188			781	1127	1908	y		y			
25	12	28/01/2003	139			702	1440	2138	y		y			
25	13	29/01/2003	109			997	1522	2516	y		y			
25	14	30/01/2003	87			727	1184	1911	y		y			
25	15	31/01/2003								y	y			

Patient	26
Age	77 years
Sex	Female
Reason for admission	post op, abdomen
APACHE II	13
Predicted mortality	16.4%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
26	0	15/02/2003							y		y			
26	1	16/02/2003							y		y			
26	2	17/02/2003							y		y			
26	3	18/02/2003							y		y			
26	4	19/02/2003	178			209	803	1011	y		y			
26	5	20/02/2003							y		y			
26	6	21/02/2003	149			295	889	1184	y		y			
26	7	22/02/2003							y		y			
26	8	23/02/2003							y		y			
26	9	24/02/2003	231			615	1055	1666	y		y			
26	10	25/02/2003	264			464	1188	1652	y		y			
26	11	26/02/2003							y		y			
26	12	27/02/2003							y		y			

Patient	27
Age	75 years
Sex	Female
Reason for admission	pancreatitis
APACHE II	27
Predicted mortality	71.6%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
27	0	02/03/2003							y		y			
27	1	03/03/2003							y		y			
27	2	04/03/2003	337			202	882	1083	y		y			
27	3	05/03/2003							y		y			Y
27	4	06/03/2003							y		y			Y
27	5	07/03/2003	266			259	785	1044	y		y			Y
27	6	08/03/2003							y		y			Y
27	7	09/03/2003							y		y			Y
27	8	10/03/2003							y		y		y	Y
27	9	11/03/2003							y		y		y	Y
27	10	12/03/2003							y		y		y	y
27	11	13/03/2003							y		y		y	y
27	12	14/03/2003								y	y		y	y
27	13	15/03/2003								y	y		y	y
27	14	16/03/2003								y	y		y	y
27	15	17/03/2003								y	y		y	y
27	16	18/03/2003								y	y		y	y
27	17	19/03/2003								y	y			y
27	18	20/03/2003								y	y			
27	19	21/03/2003								y	y			y
27	20	22/03/2003								y	y			y

27	21	23/03/2003								y	y			y
27	23	24/03/2003								y	y		y	y
27	24	25/03/2003								y	y		y	y
27	25	26/03/2003								y	y		y	y
27	26	27/03/2003								y	y		y	y
27	27	28/03/2003								y	y		y	y
27	28	29/03/2003								y	y		y	y
27	29	30/03/2003								y	y			
27	30	31/03/2003								y	y			y
27	31	01/04/2003								y	y			y
27	32	02/04/2003								y	y			y
27	33	03/04/2003								y	y			y
27	34	04/04/2003								y	y			y
27	35	05/04/2003								y	y		y	y
27	36	06/04/2003								y	y		y	y
27	37	07/04/2003								y	y		y	y
27	38	08/04/2003								y	y		y	y
27	39	09/04/2003								y	y		y	y
27	40	10/04/2003								y	y		y	y
27	41	11/04/2003								y	y		y	
27	42	12/04/2003								y	y		y	
27	43	13/04/2003								y	y			y
27	44	14/04/2003								y	y		y	
27	45	15/04/2003								y	y		y	y
27	46	16/04/2003								y	y			
27	47	17/04/2003								y	y			
27	48	18/04/2003								y	y		y	y
27	49	19/04/2003								y	y		y	y
27	50	20/04/2003								y	y		y	
27	51	21/04/2003								y	y			
27	52	22/04/2003								y	y			

27	53	23/04/2003								y	y			
27	54	24/04/2003								y	y			
27	55	25/04/2003								y	y			
27	56	26/04/2003								y	y			
27	57	27/04/2003								y	y			
27	58	28/04/2003								y	y			
27	59	29/04/2003								y	y			
27	60	30/04/2003								y	y			
27	61	01/05/2003								y	y		y	
27	62	02/05/2003								y	y			
27	63	03/05/2003								y	y			

Patient	28
Age	82 years
Sex	Female
Reason for admission	post op, abdomen
APACHE II	22
Predicted mortality	42.1%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
28	0	12/04/2003							y		y			
28	1	13/04/2003							y		y			
28	2	14/04/2003							y		y			
28	3	15/04/2003	111			425	1166	1591	y		y			
28	4	16/04/2003	73			389	1004	1393	y		y			
28	5	17/04/2003	68			371	914	1285	y		y			
28	6	18/04/2003							y		y			
28	7	19/04/2003							y		y			
28	8	20/04/2003	176			572	1393	1965	y		y			
28	9	21/04/2003							y		y			
28	10	22/04/2003							y		y			
28	11	23/04/2003							y		y			
28	12	24/04/2003	107			626	1141	1767	y		y			
28	13	25/04/2003							y		y			
28	14	26/04/2003												

Patient	29
Age	71 years
Sex	Male
Reason for admission	post op, abdomen
APACHE II	34
Predicted mortality	80.7%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
29	0	15/04/2003							y		y		y	
29	1	16/04/2003	65			407	889	1292	y		y		y	
29	2	17/04/2003	146			403	860	1263	y		y		y	
29	3	18/04/2003							y		y		y	Y
29	4	19/04/2003							y		y		y	Y
29	5	20/04/2003	157			680	1245	1922	y		y		y	Y
29	6	21/04/2003							y		y		y	
29	7	22/04/2003							y		y			
29	8	23/04/2003	95			439	1105	1544	y		y			
29	9	24/04/2003	77			439	1310	1749	y		y			
29	10	25/04/2003	53			378	2113	2491	y		y			

Patient	30
Age	30 years
Sex	Male
Reason for admission	post op, plastics
APACHE II	13
Predicted mortality	16.5%
Outcome	death

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
30	0	20/04/2003	390			1163	1303	2466		y	y			
30	1	21/04/2003								y	y			
30	2	22/04/2003								y	y			
30	3	23/04/2003	292			1436	2098	3531		y	y			
30	4	24/04/2003	232			1022	1566	2588		y	y			
30	5	25/04/2003								y	y			
30	6	26/04/2003								y	y			
30	7	27/04/2003								y	y			
30	8	28/04/2003	250			475	1260	1735		y	y			
30	9	29/04/2003	193			759	576	1335		y	y		y	Y
30	10	30/04/2003								y	y		y	Y
30	11	01/05/2003								y	y		y	Y
30	12	02/05/2003								y	y		y	Y
30	13	03/05/2003								y	y		y	Y
30	14	04/05/2003								y	y		y	Y
30	15	05/05/2003								y	y		y	Y

Patient	31
Age	72 years
Sex	Male
Reason for admission	post op, vascular
APACHE II	33
Predicted mortality	78.6%
Outcome	survivor

Patient	Day	Date	CRP	Albumin	WCC	HABF	PVBF	TLBF	Intubated	Trachy	Ventilated	PA Cath	Inotrope	Renal
31	0	31/05/2003							y		y			
31	1	01/06/2003							y		y			
31	2	02/06/2003							y		y			
31	3	03/06/2003							y		y			
31	4	04/06/2003	154			371	1623	1994	y		y			
31	5	05/06/2003	168			648	2203	2847	y		y			