Liver failure following partial hepatectomy

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Abstract
While major liver resections have become increasingly safe due to better understanding of anatomy and refinement of operative techniques, liver failure following partial hepatectomy still occurs from time to time and remains incompletely understood. Observationally, certain high-risk circumstances exist, namely, massive resection with small liver remnants, preexisting liver disease, and advancing age, where liver failure is more likely to happen. Upon review of available clinical and experimental studies, an interplay of factors such as impaired regeneration, oxidative stress, preferential triggering of apoptotic pathways, decreased oxygen availability, heightened energy-dependent metabolic demands, and energy-consuming inflammatory stimuli work to produce failing hepatocellular functions.

Key Words: Liver, hepatectomy, liver failure, liver resection

Background
Among all organs, the liver is unique in its ability to repair itself after suffering loss of tissue mass from toxins, infectious agents or surgical resection. This regenerative capacity has made it possible for surgeons to remove large portions of liver without permanent impairment of function. From the first descriptions by Keen in 1899 [1] of major hepatic resections for tumors, the postoperative course of these patients was largely uneventful, provided that they survived the operation. Mortality was high (almost 15% in 74 patients), usually from bleeding, and few, if any, of the deaths seemed to be due to liver failure. With a clearer understanding of hepatic anatomy [2], and refinements in operative technique [3,4], liver resection became more commonplace. Foster and Berman [5], in their 1974 liver tumor survey, examined 621 patients who had undergone liver resection in 98 different hospitals. The overall mortality rate was 13%. Upon reviewing the deaths, the authors found that 29 patients succumbed to “liver failure”, most within 30 days of operation. Fourteen of these deaths were thought to be due to technical causes, usually removal of “too much” liver or vascular compromise to remnant liver, and 12 deaths were in patients with cirrhosis. Three cases of liver failure could not be explained. More recent clinical series cast a similar light. In a series of over 400 partial hepatectomies, Iwatsuki and Starzl [6] detailed 19 in-hospital deaths. Eleven of these deaths were due to liver failure, nine after the first postoperative week and six after 1 month. In this group of 11 patients, 8 had undergone extended right hepatectomy (trisegmentectomy) and 7 were over 60 years of age. Savage and Malt [7] published a large series of hepatectomies, 75% of which were major, in which 12 patients died of liver failure (and five from septicemia) and 14 developed reversible liver insufficiency. Scheel and Stangl [8] observed a greater chance of liver failure in non-cirrhotics (11.5%) if more than 50% of functioning liver was removed—resulting in 5 (of 18) deaths—than if less were resected (1.3%). The dangers of extended hepatic resections, during which well over half of the liver was removed, were illustrated by Melendez and co-authors [9]. They encountered 14 postoperative deaths in these patients, 6 from sepsis and 3 from liver failure. Others [10] noted similar findings, observing that sepsis and liver failure accounted for five of seven postoperative deaths.

The interplay of clinical factors that predispose to liver failure following partial hepatectomy is the subject of this review. We will examine a number of clinical situations, which might shed light on causes of
liver failure following resection and delve into experimental data that could help to explain some of the clinical observations.

**Definition**

There is no clear definition of liver failure following partial hepatectomy. In clinical series there is even some confusion regarding cause of death, whether liver failure, sepsis, or multi-organ failure, all of which may have in common progressive liver dysfunction. Of course, liver failure may be said to occur if, following partial hepatectomy, a patient dies with deepening jaundice, worsening coagulopathy, and encephalopathy. One may refer to the definition of “acute” or “fulminant” liver failure as suggested by Hoofnagle [11] and Bernau & Benhamou [12] consisting of a progressive hyperbilirubinemia, derangements of synthetic function manifest by a decrease in hepatic dependent clotting factors, and appearance of encephalopathy, which lead to death or eventual recovery. Clinicians often recognize a normalization of the serum bilirubin for the first few days following partial hepatectomy, but then a steady increase in bilirubin accompanied by other signs of liver insufficiency. This may correspond to a failure of the regenerative process, as peak DNA synthesis occurs at about 7 days in humans [13]. While there may be an early and transient increase in total serum bilirubin for the first few days after partial hepatectomy normally, a sustained and progressive rise may signal significant dysfunction, especially when coupled with encephalopathic behavior. Histopathologically, some have classified liver failure following hepatectomy as two types: cholestatic, characterized by bile plugging, hepatocyte regeneration, and fibrosis in Disse’s space; and nonregenerative, characterized by apoptosis of hepatocytes [14]. While liver failure may be fulminant, with death occurring within days, often the onset is insidious, and deterioration of hepatic function extends over weeks before either proving fatal or improving.

**The liver and ischemia**

In the usual course of limited inflow occlusion during partial hepatectomy, it is unlikely that ischemia alone is sufficient to produce enough hepatocellular injury to cause dysfunction. The liver is remarkably resistant to normothermic ischemia. In-flow occlusion, the so-called Pringle maneuver, has been used to control parenchymal bleeding for periods of up to 1 hour with little detectable penalty [15]. In fact, the maneuver is commonly done for hepatic resections to reduce bleeding. That some degree of cellular damage occurs is manifested by modest and transient rises in serum transaminases but without clinical evidence of dysfunction. A less common maneuver to control blood loss is total vascular exclusion (TVE). The first report of TVE, clamping of in-flow and out-flow (inferior vena cava or individual hepatic veins), for up to 38 minutes, was described by Huguet and associates [16] in nine patients undergoing partial hepaectomy without a death. Henri Bismuth and colleagues [17] employed TVE and demonstrated the resiliency of the liver to normothermic ischemia in 51 patients with occlusive periods averaging 50 minutes. There was only one postoperative death in a patient with fatty liver, and no clinically significant liver dysfunction was reported in any of the survivors. Huguet and his co-workers [18] published a follow-up study to their initial work compiling a series of 59 patients, this time with ischemic periods exceeding 1 hour with only one death in a patient who developed portal vein thrombosis and liver failure. Intra-operative and postoperative biopsies showed no immediate or long-term derangement of hepatic architecture by light microscopy. By electron microscopy, warm ischemic times of approximately 30 minutes produced collapse of sinusoids, focal chromatin condensation at the nuclear margin of hepatocytes, and mitochondrial and endoplasmic reticulum swelling, but these changes were reversible on reperfusion [19]. Nevertheless, the liver is not immune to ischemia. Champion and co-authors [20] studied 19 patients after prolonged periods of hemorrhagic shock. Hyperbilirubinemia was seen 8–10 days afterwards associated with intracellular lipid deposition, perportal necrosis, acute and chronic cellular infiltrate, and bile plugging. The additional insult of infection caused maximum hepatic dysfunction, which often led to multi-system organ failure. Why, in this setting, histopathologic injury was so obvious is not clear unless the splanchnic response to hypovolemia, with its intense vasoconstriction, extends beyond the observable period of shock and produces periods of ischemia well in excess of the hour ischemic times used in more controlled surgical situations.

**Remnant liver volume**

Clinical investigations found that, following removal of up to 50% of functioning liver, there was usually only a mild and short-lived increase in serum bilirubin and depression of serum proteins—both visceral and acute phase—indicating sustained conservation of hepatocellular function [6–8,21–23]. In fact, removal of up to 75% of the liver was tolerated in most patients. However, it would be advantageous to estimate the size of the liver remnant after partial hepatectomy to reduce chances of liver insufficiency. Heymsfield and colleagues [24] first described volumetric measurements of liver in 1979 using computerized tomography (CT). In this method serial abdominal transverse cuts taken at 0.5–1.0-cm intervals were utilized, the liver being traced with a cursor, and the segments and sectors of the liver defined by right, middle, and left hepatic veins and portal vein bifurcations. The total liver volume and segmental volumes could then be calculated in milliliters. This technique was initially...
Liver volume was expressed as ml/m² body surface area. Patients who had volumetric studies prior to resection. Shirabe and associates [27] reported a series of 80 normal liver function pre-operatively. In further trials, functional liver was well tolerated in those who had reduced poor outcomes in the swine model [33], with Experimentally, the use of small allografts has proven practicable in living donor hepatic transplantation [25], with application to living donor hepatic transplantation [25], but Kubota and co-workers [26] investigated its usefulness in resections of hepatic tumors. The amount of functioning liver remaining after resection was expressed as a ratio of remnant to total liver volume.

In a series of 50 patients, resection of up to 50–60% of functional liver was well tolerated in those who had normal liver function pre-operatively. In further trials, Shirabe and associates [27] reported a series of 80 patients who had volumetric studies prior to resection. Liver volume was expressed as ml/m² body surface area. There were seven patients who developed liver failure post-operatively. The mean liver volume in these seven patients was significantly less (163 ± 63 vs 335 ± 112 ml/m², p = 0.0002), and in those with liver failure the liver volume was never more than 250 ml/m². Others [28] have found major hepatectomies to be safe with remnant liver volumes at least 25% of pre-operative values or measured size of approximately 318 cm³ [29]. With the presence of steatosis, 30% or more of the remnant liver should remain (D. Azoulay, personal communication).

Reduction in liver size apparently alters hepatic microcirculation. Kin and colleagues [30] observed a decrease in portal flow velocity and increase in hepatic artery resistive index in patients developing liver dysfunction following partial hepatectomy. Experimentally, creation of a surgical model of acute liver failure, a 90% hepatectomy in the rat model, produced an immediate decrease in hepatic microcirculatory flow and caused a remarkable increase in hepatic vascular resistance leading to liver dysfunction and failure, mirroring clinical findings. This could be partially reversed by a portal-systemic shunt [31]. From these observations, it appears that a critical reduction in liver mass leads to sudden portal hypertension, microcirculatory ischemia, reduced oxygen delivery, and hepatocellular dysfunction.

Observations in small-for-size liver transplantation may also shed some light on mechanisms of liver failure. Clinical experience has shown that the use of allografts with a graft-to-recipient weight ratio (GRWR) of <1% leads to lower graft survival [32]. Experimentally, the use of small allografts has produced poor outcomes in the swine model [33], with severe ischemic changes and hyperemia seen histologically. In the rat model [34], using allografts <30% of recipient weight, there was a transient increase in portal pressure and an increase in hepatic microcirculatory blood flow. Again, histologically, there was sinusoidal congestion and swelling of mitochondria. Modulation of portal inflow by ligation of the splenic artery has resulted in lowering of portal and hepatic arterial flow with good graft survival [35]. Similarly, creation of a mesocaval type shunt and ligation of the superior mesenteric artery have improved survival in swine and resulted in a favorable outcome in one patient with a GRWR <1% [36]. It appears, then, that high portal and hepatic artery flows to small liver remnants are inherently detrimental and contribute to alteration of microcirculatory flow, congestion, and hepatocellular dysfunction.

Other factors may also be at work. Despite an increase in requirements brought on by surgical stress, there appears to be a fall in hepatic energy levels over the first 48 hours following partial hepatectomy [37,38]. In addition, Bilimoria and others [39] felt that liver failure after hepatectomy represented a failure to regenerate at a critical mass of liver tissue. Eguchi and others [40] showed that expression of hepatocyte growth factor (HGF) and c-met mRNA in remnant liver was delayed in a rat model of fulminant hepatic failure after partial hepatectomy. There was only a modest increase in weight of the remnant liver but no signs of regeneration by either BrdU uptake, proliferating cell nuclear antigen (PCNA), or presence of mitotic figures. Survivability in a 90% hepatectomy model has been thought by others [41] to hinge on the availability of glucose and normalization of blood insulin and glucagon. This may in part, be due to reconstitution of intracellular adenine nucleotides and preservation of energy-dependent functions involved in normal metabolism and new demands for cellular replication [42].

It is evident that some crucial amount of liver must remain; yet the precise mechanism for hepatocellular failure below this critical mass cannot be completely explained. Very likely, energy supply and demand are of the essence. Failure of usual metabolic tasks probably reflects an overwhelmed hepatocyte mass, which must also deal with the added burden of regeneration.

Ipsilateral atrophy and compensatory hypertrophy are recognized occurrences after portal vein ligation. Therapeutic use of this phenomenon was initially reported by Makuuchi and co-authors in 1990 [43] in 14 patients with hilar bile duct carcinoma in order to reduce postoperative morbidity and mortality after extensive liver resection. Pre-operative portal vein embolization (PVE) has been shown to increase the remnant liver size by almost one-third [44]. More recent clinical studies have shown a benefit from preoperative PVE in reducing postoperative liver failure [45], particularly in diseased livers [46]. Additionally, the number of resectable patients has increased with the use of PVE due to increases in remnant liver volume [47]. This has proven to be a useful strategy in reducing the risk of postoperative liver failure and increasing operability for liver tumors and, once again, demonstrates the importance of remnant liver size in postoperative recovery.

Aging

Age likely plays a role in survivability following partial hepatectomy. Fortner and Lincer [48] noticed a significant increase in mortality after age 65 (11.1%) and found a further increase in mortality in this age
group with extended hepatic resection (30.7%). In the 10 deaths in older patients, 6 were due to liver failure, and all had normal preoperative liver function. Similarly, Koperna and colleagues [49] described a 15% death rate in 97 patients over age 65, increasing to 25% for those over 80 years. In patients developing postoperative liver failure (n = 47) the mortality was 21%. Infectious complications were listed as a frequent postoperative problem. On the other hand, two Asian studies showed equivalent hospital mortality and morbidity in aged patients (even over 80 years) compared to their younger counterparts when resections were done for hepatocellular carcinoma [50,51], although in both these reports a minority (31% and 14%) of patients received a major liver resection.

The effect of aging on liver function is unclear. Usual laboratory values such as hepatic enzyme profiles, serum albumin, and cholesterol values seem to be well maintained over a wide age spectrum [52]. However, both basal and taurocholate-stimulated bile flow and bile acid secretion are decreased in older experimental animals compared to younger animals [53], and bile acid synthesis has been shown to decline in geriatric subjects [54]. There also seems to be a reduced capacity for acute phase protein synthesis in older patients after liver resection [55]. Furthermore, it has been shown that aged livers do not regenerate as well. Beyer and co-workers [56] established that 1-year-old rats had retarded restoration of hepatic mass (60–70%) after partial hepatectomy at 1 week compared with juvenile rats. The induction of thymidylate synthetase and thymidine kinase, rate-determining enzymes of DNA synthesis in liver regeneration, are delayed and maximum activity reduced in 60-week-old rats after two-thirds hepatectomy [57]. In humans, smaller allograft liver volumes are found at 1 week following living donor liver transplantation in donors over 50 years of age compared with younger patients [58]. While it is speculative to attribute subtle alterations of liver function and slowing of regeneration to higher rates of post-hepatectomy liver failure, diminished hepatic reserve in the elderly may prove critical after major liver resection. These livers may be more susceptible to the additive effects of small remnant liver mass, operative ischemia, or postoperative infection.

**Chronic liver disease**

The presence of cirrhosis has been associated with a higher mortality rate after major resection, at times exceeding 20% [59,60]. This was thought to be due to compromised liver function from chronic disease reducing functional liver mass. Indeed, liver failure is a common cause of death in cirrhotics, often linked to septic events. Takenaka and colleagues [59] observed that half of the patients developing post-hepatectomy liver failure had a preceding infection. Attempts to quantify preoperative hepatic reserve using the clinical classification system of Child–Pugh [61] have met with varying success [59,60], and some have advocated a histologic grading scale, finding that fibrosis was an independent risk factor for death [62]. Nevertheless, in the face of cirrhosis, the Child–Pugh system of estimating hepatic reserve continues to be a useful clinical tool to assess operative risk.

Chronic liver disease has been associated with higher risk of liver failure following partial hepatectomy. Cirrhosis and ongoing inflammatory activity have been cited as contributing factors [59,62,63]. Both serve to impede healing. An increasingly common form of liver disease, nonalcoholic fatty liver disease and the accompanying steatohepatitis, has been found to affect the risk of major liver resections [64] including postoperative liver failure. Little and co-authors [65] found a significantly greater operative mortality in patients suffering from type I or II diabetes mellitus, the majority of whom died from postoperative liver failure and were found to have steatotic changes. It is not clear why steatotic livers are more susceptible to injury. Certainly, the presence of steatosis can be detrimental to graft function both in cadaveric [66] and living donor [67] liver transplantation. The steatotic liver is more susceptible to ischemia/reperfusion injury, perhaps due to an altered sinusoidal microcirculation [68]. There also appears to be some impairment of hepatic regeneration, as demonstrated experimentally in the rat partial hepatectomy model with a delay seen in the appearance of regenerative markers such as bromodeoxyuridine [69,70].

In an attempt to identify perturbations of liver function that might lead to postoperative failure, indocyanine green elimination [71,72], elimination of hyaluronic acid [73,74], clearance of hepatic 99mTc-diethylenetriamine pentaacetic acid-galactosyl-human serum albumin (99mTc-DPTA-GSA) [75], and measurement of hepatic mitochondrial redox state [76] have been proposed. Das and colleagues [77] found that the combination of these risk factors predicted morbidity in 100% of their patients. In the setting of chronic liver disease, whether cirrhosis and/or chronic inflammation, damage to the hepatocyte probably results from regional ischemia (cirrhosis) or liberation of inflammatory mediators. That regeneration is slowed by the presence of cirrhosis has been shown in clinical studies using volumetric determinations of remnant size [21,22]. Slowed regeneration can, in part, be explained by lower levels of HGF, possibly due to failure to convert HGF precursor to the biologically active form [78]. Down-regulation of cell cycle regulators and impairment of transcription factors may also play a role [79]. This may be caused by cirrhosis-induced hypoxia affecting hepatocytes and associated mesenchymal support cells [80].

**Sepsis**

Clinically, there appears to be a strong link between sepsis and post-hepatectomy liver failure. In one series...
of 19 patients developing intraperitoneal septic complications after hepatectomy, 13 died of liver failure [81]. Experimentally, alteration of gut contents by antibiotic treatment reduced endotoxemia and mortality after two-thirds hepatectomy in rats [82]. Administration of endotoxin following hepatectomy produced massive hepatic necrosis and 50% mortality, but not in sham-operated control animals [83], and restricted liver cell proliferation, perhaps mediated by the cytokine interleukin-1 (IL-1) [84]. Neutralization of endotoxin and blocking of IL-1 reduced hepatic inflammation and reduced serum levels of transaminases in hepatectomized rats [85]. The lethality of endotoxin in such situations might be explained, in part, by Kupffer cell dysfunction. Impairment of Kupffer cell activity has been detected by a reduction in production of the hepatotropic cytokine, tumor necrosis factor-α (TNF-α), which led to retardation of regeneration [86,87]. Panis and co-authors [88] have suggested that a critical mass of remaining liver is dependent not only on the amount of functional hepatocytes but also on the number of Kupffer cells available to assist in regeneration through elaboration of initiator cytokines and clearance of portal vein endotoxin. The work of Shiratori and others [89] lent support to this theory by observing that suppression of Kupffer cells by gadolinium chloride in hepatectomized rats reduced concentrations of TNF-α and IL-6, reduced PCNA labeling of hepatocytes, and disturbed liver regeneration. Impaired clearance of endotoxin in hepatectomized rats led to multi-organ failure but could be reversed by the endotoxin-neutralizing N-terminal bactericidal/permeability-increasing protein [90]. Furthermore, translocation of enteric bacteria has been demonstrated in blood, mesenteric lymph nodes and other organs as early as 2 hours following 90% hepatectomy in rats, reflecting an inability of surviving Kupffer cells to provide adequate clearance [91]. In fact, the rate of translocation of intestinal microflora in portal and arterial blood after 70% hepatectomy was reported to be 100% at 24 hours [92]. This translocation was detected in the liver as well as other intra-abdominal organs. Return of Kupffer cell function may not normalize for over 2 weeks [93]. However, recovery of Kupffer cell activity has an impact on outcome in patients in fulminant hepatic failure, regaining steadily their ability to clear 124I-labeled microaggregated albumin in those that survived [94]. Reduced Kupffer cell mass and impaired function coupled with the enhanced permeability and availability of enteric microorganisms provides a dangerous milieu for the production and liberation of endotoxin.

Endotoxin also has a specific effect on the hepatocyte. Administration of endotoxin to pigs resulted in reduced clearance of hepatoiminodiacetic acid (HIDA) even before increases in cardiac index or decreases in systemic vascular resistance [95]. Direct contact of endotoxin with hepatocytes, perhaps through membrane receptors, caused derangements of hepatocyte function identified as lysosomal damage, decreased mitochondrial function, and impaired bile salt-independent bile flow and sulfobromophthalein excretion [96–98]. In perfused livers of endotoxemic rats, reduced clearance of bilirubin and taurocholate were found, reflecting an impairment of intracellular transport rather than altered conjugation [99]. These changes could be explained by relocation of ATP-diphosphohydrolases as a result of exposure to endotoxin [100]. Others [101] have found a decrease in synthesis of canalicular multispecific organic anion transporter protein, perhaps contributing to hyperbilirubinemia and cholestasis. This effect was mediated by Kupffer cell activation by endotoxin and elaboration of IL-1 and TNF-α. In addition, bile plugging, described microscopically in cholestatic liver failure [14], might be explained by alteration of the tight junction between hepatocyte couplets, increasing permeability and producing bile regurgitation [102]. Endotoxin has been found to impair regeneration by reducing hepatocyte growth related mRNA and depressing PCNA [76,103].

Endotoxin, then, can play a dual role in posthepatectomy liver failure. By action on the Kupffer cell there is impairment of initiator cytokines necessary for regeneration. This effect is magnified with reduction in Kupffer cell mass that accompanies extensive liver resections. At the same time endotoxin alters the internal milieu of hepatocytes by its effect on transport mechanisms, initiation of regeneration, and membrane function. The end result could be a small liver remnant with defective reticuloendothelial activity, disrupted hepatocellular metabolism, and impaired regenerative pathways.

**Regeneration**

Liver failure can be viewed as a net loss of functioning hepatocytes to the point that surviving hepatocytes cannot maintain adequate metabolic functions. This represents either a failure to regenerate after partial hepatectomy or accelerated destruction of hepatocytes from necrosis or apoptosis. Post-hepatectomy liver regeneration is a complex, but well orchestrated, series of events initiated by a number of autocrine, paracrine, and endocrine hepatotrophic factors [104]. Regeneration has most easily been studied in the rat or mouse partial hepatectomy model or in cell culture. These may not be translatable to human liver regeneration as events occur much earlier in the rodent models and cell culture methodology may not take into account the role of supporting cells, cytokines, and hepatotrophic factors found in vivo.

Proliferation of all cellular components and matrix occurs with hepatocytes, the first to begin mitotic activity. In humans with normal livers, regeneration occurs in the first 2 weeks after hepatectomy and is completed by 3 months [21,105,106]. The protooncogenes c-fos, c-jun, and c-myc are usually considered the
markers for the initial phase of regeneration [107]. These genes are expressed even after massive hepatectomy in experimental animals [108]. Simultaneously, a number of genes are expressed in the early phases of regeneration involved in control of growth [109]. In response to these molecular events, normally quiescent and highly differentiated hepatocytes enter and progress through the various stages of cell replication. Gene expression is thought to occur after activation by a number of identifiable hepatotrophic factors. Prominent among these are TNF-α, HGF, epidermal growth factor (EGF), transforming growth factor-α (TGF-α), and IL-6. It appears that the cytokines TNF-α and IL-6 are early initiators of DNA synthesis in regenerating hepatocytes, although it is not clear whether their roles are facultative or triggering [110,111]. Cell cycle progression requires, in addition to these hepatotrophic factors, activation of cyclin-dependent kinases (Cdks) that are regulated by cyclins and Cdks inhibitors [112]. The Cdk inhibitor p21 has been identified as an important protein in halting liver regeneration and may be induced by the presence of the hepatocyte proliferative inhibitor transforming growth factor-β (TGF-β) [113,114]. Regeneration may also be halted by inhibition of nuclear factor kappa B (NFκB) [115,116]. NFκB probably prevents apoptosis by terminating activation of c-Jun NH2-terminal kinase (JNK) [117].

Part of the initial response of the remnant liver to partial hepatectomy is induction of members of the signal transducers and activators of transcription (Stat). This family of factors participates in the regulation of growth response genes and is induced early following partial hepatectomy [118]. Experimentally, in fatty livers, induction of Cdks after partial hepatectomy is abolished, alteration of Stat-3 occurs, and adenosine triphosphate levels are reduced, which arrests hepatocyte proliferation and impairs regeneration [119]. In fact, others [120] have found hyperinduction of Stat-3 after liver injury in obese mice, which impairs regeneration by up-regulating mechanisms that impede progression of the cell cycle. Interference in the regenerative pathways, either by suppression of hepatotrophic factors or by up-regulation of cell cycle inhibitors (or both), may help explain failure of the remnant liver to sustain metabolic functions.

It is now apparent that nitric oxide (NO) plays an important role in liver regeneration. Generation of NO is dependent on cytokine inducible nitric oxide synthase (iNOS). Levels of iNOS are elevated after partial hepatectomy in the rat model [121]. In transgenic mice with targeted disruption of the iNOS gene, partial hepatectomy results in heightened caspase-3 activity, hepatocyte apoptosis, and liver failure [122]. One mechanism for the regenerative contribution of NO may lie in its ability to down-regulate S-adenosylmethionine synthesis, which is involved in inhibition of HGF-induced cyclin D1 and D2 expression [123]. Therefore, any disruption of NO synthesis would seem to have a deleterious effect on regeneration and may, in fact, uncover apoptotic pathways.

**Apoptosis**

Liver cell loss can occur via two mechanisms: necrosis and apoptosis. Histopathologic studies of failing livers do not mention necrosis as a prominent finding and, in fact, observe apoptotic changes in some specimens [14]. Apoptosis of cells occurs from external or internal signaling. External signaling involves the cell membrane receptors, TNF-receptor 1 (TNFR1) and the Fas/Apo receptor. Binding by TNF-α or Fas ligand activates the caspase cascade, eventually resulting in cell death. While hepatocytes are rich in these cell surface receptors, activation usually results in initiation of regenerative rather than apoptotic pathways [110,124]. Despite the ability of TNF-α to trigger apoptotic events by combination with its 55-kDa TNFR1 and up-regulation of Fas/Apo 1 receptors [125,126], regenerative pathways seem to prevail even to the degree of suppressing Fas-signaling apoptotic cascades [127]. Whether apoptosis plays a significant role in loss of hepatocytes after partial hepatectomy is unclear. Lee and co-workers [128] described a three-fold rise in apoptotic cells at 1 hour following 70% hepatectomy in rats, and Sakamoto and colleagues [129] reported a “wave” of apoptosis occurring between 60 and 96 hours after 70% hepatectomies in mice. On the other hand experiments in our laboratory [130] have failed to disclose a meaningful increase in apoptotic activity following partial hepatectomy in rats even with endotoxin stimulation and high levels of TNF-α. It appears difficult, in otherwise intact experimental animals, to induce apoptosis over regeneration using commonly recognized external stimulators for “death domain” activation in survivable models of partial hepatectomy.

Internal signaling of the caspase cascade can occur from oxidative stress focused on the mitochondria. Formation of reactive oxygen species has been shown to promote apoptosis through creation of voltage-dependent anion channels in the outer mitochondrial membrane [131]. Leakage of cytochrome C through these channels then induces the entire caspase cascade, resulting in apoptosis [132]. Additionally, oxidative stress can cause perturbations of Ca2+ homeostasis and influx of the cation into the cytoplasm from outside the cell or the endoplasmic reticulum, the main intra-cellular store of Ca2+. Influx of Ca2+ can cause disruption of mitochondrial metabolism and alteration of gene transcription leading to apoptosis [133]. The focus of the anti-apoptotic protein Bcl-2 and the pro-apoptotic proteins Bax and Bak may be regulation of Ca2+ flux from the endoplasmic reticulum [134].

Aging can increase susceptibility to oxidative stress. Ikeyama and associates [135] have shown that hepatocytes from aged rats (24–26 months old) exhibited
reduced proliferative capacity when exposed to hydrogen peroxide or epidermal growth factor. These same investigators subsequently discovered that the pro-apoptotic gene gadd153 is up-regulated in aging rats and is particularly sensitive to oxidative injury [136]. Aberrant induction can also occur with stimulation by epidermal growth factor in aging rats. Others [137] have determined that the calcium-binding protein senescence marker protein-30 (SMP-30) decreases with aging. In mutant mice lacking SMP-30, hepatocytes were more susceptible to apoptosis induced by TNF-α. SMP-30 could be considered an anti-apoptotic protein that, with age and decreasing levels, is less able to prevent progression of apoptotic events initiated by external signals.

Summary

Liver failure following partial hepatectomy is more likely to occur in certain clinical situations. Important parameters to consider include functional mass of remnant liver, the age of the patient, and the presence of pre-existing liver disease such as cirrhosis, chronic hepatitis, and fatty liver disease. Postoperative infection can be equally damaging to a regenerating liver. Each of these conditions interferes with the normal regenerative pathways and/or initiates apoptotic pathways, resulting in a net loss of functional hepatocytes. The cellular mechanism for liver failure appears may be the preferential triggering of caspase-dependent apoptotic pathways, more likely from internal signaling rather than external receptor activation, as well as down-regulation of the myriad of regenerative factors involved in moving the resting hepatocyte through its cell cycle. In particular, the aging process may be responsible for heightened oxidative stress and susceptibility to cytochrome release from mitochondria, in metabolically active hepatocytes after partial hepatectomy, thus providing another pathway for caspase activation. In the clinical arena attention to factors that can reduce chances of liver failure following partial hepatectomy, especially provision of adequate liver remnant, avoidance of major hepatectomy in the cirrhotic patient, and caution when embarking on resections in the steatotic liver, should improve outcome. It is important for the liver surgeon to appreciate the effect of sepsis on the remnant liver and expeditiously address infectious problems that may occur postoperatively.

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