The Impact of Aging on the Liver

David Stell, PhD, FRCS(Gen) and William J. Wall, MD, FRCS(C), Department of Surgery and Multi-Organ Transplant Program, London Health Sciences Centre, London, ON.

The process of aging does not produce changes in the liver that can be described as pathological. The major age-related alterations are a reduction in liver mass and a reduction in total blood flow, neither of which interferes with the liver's normal homeostatic functions. In spite of the liver's resilience, however, the aged liver is more vulnerable to injury from toxins, viruses and ischemia, and its capacity to regenerate is slowed. There also is a decline in liver enzymes with aging that affects metabolic clearance of drugs, a finding that has implications for drug dosing in the elderly.

Key words: liver, aging, function, metabolism, injury.

Introduction

The liver is a resilient organ that maintains its homeostatic functions with age. Routine tests of liver function (serum bilirubin, serum albumin, aminotransferases, alkaline phosphatase and INR) remain normal in the healthy elderly.[1] Unlike the heart, brain and kidneys, the liver is not affected by common degenerative diseases such as atherosclerosis, diabetes and hypertension. The liver is spared these diseases probably as a result of its dual blood supply, abundant reserve and regenerative capacity.[2] Nevertheless, certain age-related changes do occur in the senescent liver that deserve consideration.

Morphology and Physiology

The characteristic gross change that occurs in the aging liver is "brown atrophy". The darkened colour is due to accumulation of lipofuscin pigment within hepatocytes. Liver mass declines relative to body mass, a change that is accompanied by a decrease in total hepatic blood flow.[3] A recent study has suggested a discrepancy between the decrease in size measured by computed tomography and the total hepatocyte cell mass. Using radio-labelled albumin as a marker of functioning hepatocytes, Wakabayashi, *et al.* showed an exaggerated decline in functional hepatocyte mass even when accounting for the decline in total liver size with age.[4] The decline in liver blood flow in this study correlated with the decrease in functional hepatocyte mass rather than the total liver volume, suggesting that blood flow per hepatocyte remains unchanged with age. Dynamic tests of hepatic function show a decline with age. The hepatic elimination of galactose and caffeine is significantly reduced in the elderly population,[5] in keeping with the reduction in hepatocyte mass.

At the microcirculatory level, liver sinusoids demonstrate endothelial thickening and loss of fenestrations, referred to as pseudocapillarisation.[6] Kupffer cells, important in the elimination of endotoxin and tumour cells, suffer a decline in phagocytic function with aging.[7] At the ultrastructural level, hepatocytes demonstrate a decline in rough endoplasmic reticulum and mitochondria.[8]

Response to Injury

The liver is generally quite tolerant of both acute and chronic insults. It is capable of recovering from interruption of its blood supply and oxygenation for periods lasting one hour.[9,10] However, as the liver ages, its ability to regenerate after toxic injury is impaired—the regenerative response is complete but it takes longer.[11,12] Clinical experience has shown that mortality after fulminant hepatic failure is higher in the aged population regardless of the etiology of the hepatic injury,[13] although mechanisms other than impaired hepatic regeneration may contribute.

The reduced ability of the older liver to regenerate may have an impact on the natural history of some liver diseases. The rate of progression to cirrhosis in patients with chronic hepatitis C is directly associated with age at the time of contracting the infection.[14] This finding agrees with the observation that livers from older donors that are transplanted into hepatitis C-infected recipients are more likely to be damaged by the virus compared to younger grafts.[15] The delayed regenerative response does not prevent major hepatic resection in the elderly patient, however. Resection of over 50% of hepatic volume is compatible with a full recovery in the elderly, and the risks of hepatic surgery in this age group are determined by comorbidities, such as cardiovascular disease.[16,17]

Liver transplantation has benefited from the liver's resilience, and has provided insight into the ability of the liver to recover from preservation injury. Livers from elderly donors (older than 70 years) will function successfully after transplantation, a procedure that requires an obligatory period of liver storage at near freezing temperatures.[18,19] Experimental studies have shown that aged livers are more susceptible to cold preservation injury than young livers, leading to the recommendation that the preservation period should be kept as short as possible.[20] Experimental

Table 1 Phases of Drug Metabolism

	Phase I	Phase II
Action	Oxidation, reduction hydrolysis	Glucuronidation and methylation
Location	Smooth endoplasmic reticulum	Cytosol
Reduced in aging	Yes	Unknown
Commonly used drugs affected in the elderly	– anticonvulsants – calcium-channel antagonists – non-steroidal anti-inflammatories – some antihypertensives	

liver grafts in rats have demonstrated that the liver can not only survive for exceptionally long periods of time, but that it continues to perform its normal metabolic functions even when it has survived far beyond the maximum recorded life-span for rodents.[21] The "bioprolonged" livers demonstrate more pronounced histological features of aging, but the organs did not develop pathological changes.

Influence of Age on Common Liver Diseases

Age has a variable impact on other common liver diseases. Cirrhosis normally develops after many years of alcohol abuse and the peak incidence of presentation with alcoholic cirrhosis is in the seventh decade.[22] The complications of alcoholic liver disease also are more severe in the elderly; one study of alcoholic cirrhotic patients has shown an annual mortality rate of 50% among patients older than 60 years, compared to 7% in patients younger than 60.[23] Similarly, primary biliary cirrhosis most commonly presents in women in the sixth decade, and once symptoms develop, most series have shown that increasing age has an adverse effect on patient survival.[24] Autoimmune liver diseases, however, generally affect younger women, and two series have shown that only 20% of cases of autoimmune hepatitis occur in patients older than 65 years, an age group in which the diagnosis is often delayed.[25,26] The prognosis in this age group is excellent however, as the disease generally follows a more benign course that rarely leads to cirrhosis.[25]

Drug Metabolism in the Elderly

Drug metabolism by the liver can be broadly divided into two phases (Table 1). Phase I involves oxidation, reduction and hydrolysis and serves to make compounds more hydrophilic, while Phase II reactions add glucuronide or methyl groups to assist in renal elimination.[27] Phase I reactions are performed by enzymes of the cytochrome P450 system and occur in the smooth endoplasmic reticulum of hepatocytes, whereas Phase II reactions occur in the cytosol. Most studies of hepatic drug metabolism in the elderly have addressed changes in Phase I enzymes.

A study of liver biopsies from a large, heterogenous population has shown a gradual decline in the hepatocyte concentration of P450 enzymes with age.[28] Furthermore, these microsomal enzyme reactions are oxygen-dependent, so will be affected by the relative hypoxia which follows pseudocapillarisation of the hepatic sinusoids with age.[29] These findings, along with the decline in hepatocyte mass and hepatic blood flow in the elderly, explain the reduced clearance of many drugs in this population. This is an important consideration when prescribing drugs to the elderly that are metabolised predominantly by the liver, such as anticonvulsants[30] and calcium-channel antagonists.[31] An important consideration in caring for the elderly is the high incidence of polypharmacy and drug reactions in this age group, so that in general, lower doses of hepatically-metabolised drugs are indicated compared to a younger age group. ◆

No competing financial interests declared.

References

1. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals—sexagenarians through centenarians. Clin Chem 1992;38:1167-85.
2. Popper H. Aging and the liver. Prog Liver Dis 1986;8:659-83.
3. Wynne HA, Cope LH, Mutch EWynn, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 1989;9:297-301.
4. Wakabayashi H, Nishiyama Y, Ushiyama T, et al. Evaluation of the effect of age on functioning hepatocyte mass and liver blood flow using liver scintigraphy in preoperative estimations for surgical patients: comparison with CT volumetry. J Surg Res 2002;106:246-53.
5. Schnegg M, Lauterburg BH. Quantitative liver function in the elderly assessed by galactose elimination capacity, aminopyrine demethylation and caffeine clearance. J Hepatol 1986;3:164-71.
6. Le Couteur DG, Cogger VC, Markus AM, et al. Pseudocapillarization and associated energy limitation in the aged rat liver. Hepatology 2001;33:537-43.
7. Brouwer A, Barelds RJ, Knook DL. Age-related changes in the endocytic capacity of rat liver Kupffer and endothelial cells. Hepatology 1985;5:362-6.
8. Schmucker DL. Aging and the liver: an update. J Gerontol A Biol Sci Med Sci 1998;53:315-20.
9. Harris KA, Wallace C, Wall WJ. Tolerance of the liver to ischaemia in the pig. J Surg Res 1982;33:524-30.
10. Quan D, Wall WJ. The safety of continuous hepatic in flow occlusion during major liver resection. Liver Trans and Surg 1966;2:99-104.
11. Schapiro H, Hotta SS, Outten WE, et al. The effect of aging on rat liver regeneration. Experientia 1982;38:1075-6.
12. Sanz N, Diez-Fernandez C, Cascales M. Aging delays the post-necrotic restoration of liver function. Biofactors 1998;8:103-9.
13. Forbes A, Williams R. Increasing age—an important adverse prognostic factor in hepatitis A virus infection. J R Coll Physicians Lond 1988;22:237-9.
14. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-32.
15. Berenguer M, Prieto M, San Juan F, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected transplant recipients. Hepatology 2002;36:202-10.
16. Takenaka K, Shimada M, Higashi H, et al. Liver resection for hepatocellular carcinoma in the elderly. Arch Surg 1994;129:846-50.
17. Fong Y, Blumgart LH, Fortner JG, et al. Pancreatic or liver resection for malignancy is safe and effective for the elderly. Ann Surg 1995;222:426-34; discussion 434-7.
18. Wall W, Grant D, Roy A, et al. Elderly liver donor. Lancet 1993;341-6.
19. Emre S, Schwartz ME, Altaca G, et al. Safe use of hepatic allografts from donors older than 70 years. Transplantation 1996;62:62-5.
20. Sakai Y, Zhong R, Garcia B, et al. Tolerance by old livers of prolonged periods of preservation in the rat. Transplantation 1993;55:18-23.
21. Sakai Y, Zhong R, Garcia B, et al. Assessment of the longevity of the liver using a rat transplant model. Hepatology 1997;25:421-5.
22. James OF. Parenchymal liver disease in the elderly. Gut 1997;41:430-2.
23. Potter JF, James OF. Clinical features and prognosis of alcoholic liver disease in respect of advancing age. Gerontology 1987;33:380-7.
24. Grambsch PM, Dickson ER, Kaplan M, et al. Extramural cross-validation of the Mayo primary biliary cirrhosis survival model establishes its generalizability. Hepatology 1989;10:846-50.
25. Newton JL, Burt AD, Park JB, et al. Autoimmune hepatitis in older patients. Age Ageing 1997;26:441-4.
26. Schramm C, Kanzler S, zum Buschenfelde KH, et al. Autoimmune hepatitis in the elderly. Am J Gastroenterol 2001;96:1587-91.
27. Tregaskis BF, Stevenson LH. Pharmacokinetics in old age. Br Med Bull 1990;46:9-21.
28. Sotaniemi EA, Arranto AJ, Pelkonen O, et al. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 1997;61:331-9.
29. Le Couteur DG, McLean AJ. The aging liver. Drug clearance and an oxygen diffusion barrier hypothesis. Clin Pharmacokinet 1998;34:359-73.
30 Bernus I, Dickinson RG, Hooper WD, et al. Anticonvulsant therapy in aged patients. Clinical pharmacokinetic considerations. Drugs Aging 1997;10:278-89.
31. Kates RE. Calcium antagonists. Pharmacokinetic properties. Drugs 1983;25:113-24.