REVIEW ARTICLE

Cardiovascular Dysfunction in Patients with End-stage Liver Disease

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Most patients with advanced liver disease have a normal or even supernormal ejection fraction judged by echocardiography. Thus, physicians previously assumed that cardiac function was normal in most patients with liver disease. However, further investigation has uncovered multiple problems in cardiac performance that place patients at risk of heart failure. Patients with liver disease have defects in both systolic and diastolic function that only become obvious with physiologic stress such as liver transplantation. In addition there are additional defects in the electromechanical coupling of the heart that can have significant clinical consequences. These collective pathologic changes are termed "cirrhotic cardiomyopathy" and occur to some degree in all patients with liver disease. This review will explore the pathophysiology of cardiovascular changes in patients with end-stage liver disease. [*J Chin Med Assoc* 2008;71(7):331–335]

Key Words: cardiac function, cardiomyopathy, liver transplantation

Body Fluid Composition in Liver Disease

Approximately 2 thirds of the total body water is normally contained in the intracellular compartment while the remaining 1 third is distributed in the intravascular and intercellular space. At any 1 point within a cardiac cycle, most of the total blood volume is found in the systemic veins with only 10% in the splanchnic circulation (Figure 1).[1,2]

The distribution of total body fluid is altered by liver disease. Sodium and water are retained by the kidneys and this increases the amount of total body fluid. Fluid shifts into the intracellular compartment, which expands to accommodate the increased volume.[3] In disease, this compartment commonly holds 3 quarters or more of the total body water.[4] Protein-rich fluid moves into the body cavities as disease worsens. This causes ascites and pleural or pericardial effusion.[5] As disease progresses, total blood volume increases but the relative amount of blood in the systemic circulation falls. Rather, blood moves into splanchnic (gut) circulation as it expands due to portal hypertension (Figure 2). Tissue oxygenation is therefore impaired.

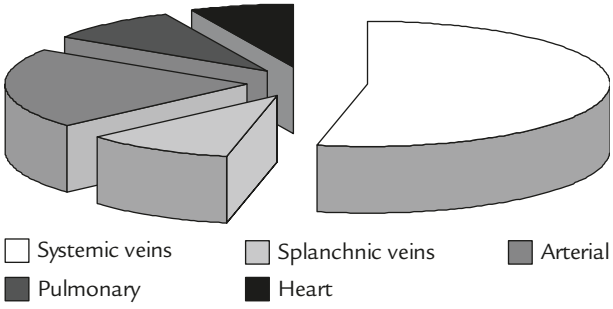

Figure 1. The normal distribution of blood in body compartments.

These changes are initiated by the development of portal hypertension. Portal hypertension causes vasodilatation and new blood vessel formation in the splanchnic circulation.[6] An increase in the number of small slow transit blood vessels in the gut increases the capacitance of the splanchnic circulation. Blood enters this low resistance circulation and becomes unavailable to the systemic circulation.[2] The resulting fall in arterial blood volume activates the arterial baroreceptors. Tonic impulses to the central nervous system from arterial baroreceptors normally inhibit the sympathetic nervous

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E-mail: mytsou@vghtpe.gov.tw • Received: December 27, 2007 • Accepted: April 24, 2008

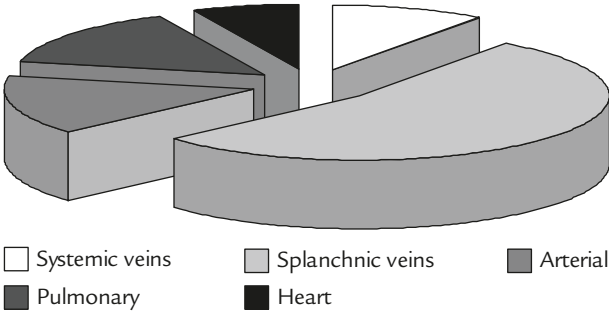

Figure 2. The distribution of blood volume in patients with portal hypertension.

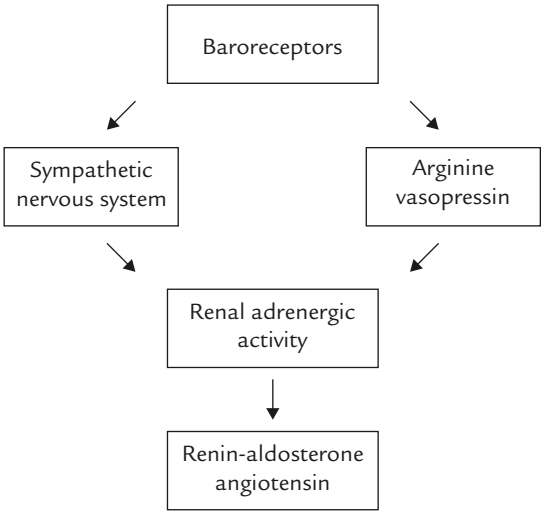

Figure 3. The neurohormonal reflex that causes an increase in renal water and solute absorption.

system and the nonosmotic secretion of arginine vasopressin.[7] A fall in arterial pressure causes a loss of arterial baroreceptor activity. In turn, this triggers an increase in sympathetic nervous system activity and arginine vasopressin is secreted. The resulting increase in renal adrenergic activity reduces the amount of water and sodium delivered to the collecting duct of the kidneys. The latter causes the kidney to secrete renin, arginine vasopressin and natriuretic peptide (Figure 3).

Normally, this neurohormonal pathway restores circulating blood volume. However, portal hypertension is progressive and therefore the capacity of the splanchnic circulation increases with under-filling of the arterial circulation. This continues to drive the neurohormonal response that causes the retention of sodium water and other solutes even though total body water and sodium is increased. The reduced solute delivery to the kidney is such a strong stimulus that the sodium-retaining effects of aldosterone predominate over the diuretic effects of natriuretic peptide. Total body fluid homeostasis can only be restored by the effective treatment of portal hypertension.[6]

Heart Disease in Cirrhosis

Physicians previously thought that heart disease was rare in patients with cirrhosis.[8] They hypothesized that better lipid profiles, reduced blood clot formation and lower blood pressures in cirrhotic patients reduced cardiac complications. Further, few perioperative cardiovascular complications were observed in the early history of transplantation. However, postoperative mortality at that time was primarily due to operative complications and poor donor graft function. Better surgical technique and donor organ management significantly improved overall patient outcome. As long-term patient survival improved, cardiac complications emerged as a more common cause of early morbidly and mortality. Recent studies report radiographic evidence of pulmonary edema with hypoxemia and overt congestive heart failure in as many as 56% and 5.6% of all perioperative transplant recipients, respectively.[9,10] It is also remarkable that hemodynamically significant cardiac arrhythmias are reported in up to 27% of transplant recipients following surgery.[10]

Ischemic heart disease

Even though cirrhotic patients have more cardiovascular complications than the general public, the preoperative diagnosis of cardiac disease is still difficult. Patients with advanced and end-stage liver disease usually have poor exercise capacity. Consequently, they may not experience common symptoms that are usually provoked by exercise such as chest pain or shortness of breath. Further, it may be impossible to determine if some symptoms such as shortness of breath are caused by cardiac or liver disease. The exact prevalence of angiographically proven critical coronary artery stenosis (>50%) in liver transplant candidates is unknown. However, the evidence suggests that coronary artery disease (CAD) is more prevalent in transplant candidates. Generally, investigators report that at least 1 critical coronary artery lesion occurs in 5–26% of all liver transplant candidates who are asymptomatic.[11–14] Of these patients, up to 50% with significant CAD will die perioperatively from cardiac complications.[12] This is substantially greater than the 1-year mortality rate (10%) for all liver transplant recipients[15] or the mortality rate from cardiac complications for other study populations.[16,17] The latter makes the identification of CAD prior to transplantation a precedent. A previous history or classic symptoms of CAD place

patients in well-tested protocols that direct further evaluation.[18,19] However, the challenge remains in identifying those patients who are asymptomatic but have significant CAD.

Cardiomyopathy

The prevalence of cardiomyopathy is greater in patients with end-stage liver disease than in the general population.[20,21] Conditions such as hepatitis C can cause immune-mediated myocarditis and fibrosis resulting in restrictive cardiomyopathy.[21] Hemochromatosis and amyloidosis also cause restrictive cardiomyopathy due to the infiltration of iron and protein respectively.[22,23] Findings similar to dilated cardiomyopathy are also commonly reported from routine echocardiographic screening of transplant candidates.[20] Further, an increased reporting of hypertrophic cardiomyopathy in transplant candidates suggests that this disorder may also be more prevalent in cirrhotic patients.[24,25]

Cirrhotic cardiomyopathy

Some cirrhotic patients have obvious feature of cardiomyopathy. However, most have a normal or even supernormal ejection fraction judged by echocardiography. Thus, physicians often assume that cardiac function is normal in these patients. However, further investigation has uncovered multiple problems in cardiac performance that place patients at risk of heart failure. Early cardiac decompensation is often missed because the cardiac workload is reduced by peripheral vasodilatation caused by liver failure.[26] Thus, cirrhotic patients are dismissed as having normal heart function. However, when these patients are subject to physiologic or pharmacologic stress, they develop clinical signs of suboptimal perfusion including renal failure and acidosis. Investigators have concluded that exercise uncovers an intrinsic defect in myocardial function that predisposes to heart failure.[27,28]

Most patients with liver disease have subtle defects in myocardial function that are not apparent on cursory examination. Defects in both systolic and diastolic function only become obvious with physiologic stress such as liver transplantation.[29] This condition is termed "cirrhotic cardiomyopathy" and, although the clinical presentation can be variable, all patients have 4 common features. These are: (1) baseline increased cardiac output; (2) attenuated systolic contraction and diastolic relaxation; (3) electrophysiologic abnormalities including repolarization change; and (4) a reduced response of the heart to direct beta stimulation (β-incompetence).[30] These changes occur in the absence of overt congestive ventricular failure and with only modest changes such as mild chamber dilatation.

At rest, systolic function appears to be normal in most patients with liver disease. However, the mechanics of systolic contraction are commonly disturbed. This is shown by examination of the systolic time interval. The length of systole remains constant, but left ventricular ejection period takes up a larger percentage of the time interval. This in turn shortens the pre-ejection period.[31] In contrast to changes in diastole, systolic dysfunction usually only becomes evident during exercise. Ejection fraction does not increase as expected under conditions of stress. An increase in filling pressures does not increase ejection fraction as expected and the Frank Starling curve flattens. As liver disease progresses, systolic function can be insufficient to meet tissue oxygen demands even at rest.[32] The impaired systolic response to stress is etiologic in the increased incidence of pulmonary edema and congestive heart failure following procedures that abruptly increase blood flow to the heart.

Early histologic changes in cirrhotic hearts include myocardial hypertrophy, interstitial and cellular edema, and signs of cellular injury.[33] This causes global thickening of the left ventricle with the septum affected more than the free wall.[29] Overall, these effects are more pronounced in patients with ascites compared to those without. As wall thickness increases, so does the degree of diastolic dysfunction. Impaired diastolic relaxation prolongs isovolumetric relaxation and also produces a steep compliance curve where the ventricular pressure is greater than normal for any given end diastolic volume. The left atrium dilates in response to the higher impedance to left ventricular filling. When patients are exposed to acute changes in circulation that rapidly increase filling pressure, they are at risk of developing congestive heart failure. This accounts for the high incidence of congestive heart failure after procedures such as transjugular intrahepatic shunts and liver transplantation.[34] In fact, diastolic disturbance is such a consistent feature of cirrhotic cardiomyopathy that many investigators suggest that some degree of diastolic dysfunction is present in all patients with liver disease.

Patients with liver disease exhibit 3 common cardiac electrophysiologic disturbances in cardiac function. These include: (1) electromechanical dissociation; (2) prolongation of ventricular polarization (the QT interval); and (3) chronotropic incompetence.[33] The time period between electrical and mechanical systole is longer in patients with cirrhosis.[35] If the conducting system is still partially depolarized when the next action potential arrives, electrical depolarization cannot capture all the mechanical activity of the myocardium.

Once electromechanical dissociation becomes severe, it prolongs the time required for repolarization

(QT interval). Prolongation and variability in the QT interval can affect cardiac rhythm and cause serious disturbances including ventricular fibrillation. The severity of electromechanical dissociation is clearly related to the severity of liver disease. This is shown by the fact that the length of the QT interval correlates directly with the Child-Pugh score.[31] While patients with congenital prolonged QT appear to have defects in the sodium receptors that regulate electrical gating, the potassium gates of the conducting system are primarily affected in patients with liver disease.[36]

Chronotropic incompetence is the inability of the sinus node to increase heart rate in response to physical or metabolic stress. The conducting system is dominated by the parasympathetic system and there is a downregulation in the number and sensitivity of β-receptors. Chronotropic incompetence is an independent predictor of mortality in patients with cardiac disease. But it is not known if it also predicts mortality in patients with liver disease. However, failure to adapt heart rate to physiologic demand has important consequences in patients with liver disease. Because contractility is depressed, heart rate becomes a major determinant of cardiac output in patients with liver disease. Chronotropic incompetence explains the failure to reach target heart rates during dobutamine stress testing.

Conclusion

Cardiac disease is a common complication of liver disease that reduces post-transplant survival. Ischemic heart disease and cardiomyopathy occur more commonly in liver transplant candidates than most other surgical patients. There is still considerable debate on whether it is cost-effective to screen all transplant candidates for the presence of coronary and structural heart disease. The unusually high perioperative mortality in transplant patients who do have CAD incurs a significant price in terms of cost and the preventable loss of human organs. These considerations support a systematic evaluation of all liver transplant candidates. No single test has 100% predictive value. Therefore, diagnostic protocols must account for the variation in prevalence that occurs in subsets of transplant candidates and the limitation of each type of test.

References

1. Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med* 1990;113:155–9.
2. Schrier RW. Decreased effective blood volume in edematous disorders: what does this mean? *J Am Soc Nephrol* 2007;18: 2028–31.
3. Arroyo V, Jimenez W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. *J Hepatol* 2000;32:157–70.
4. Eisenhut M. Changes in ion transport in inflammatory disease. *J Inflamm* 2006;3:5.
5. Cardenas A, Arroyo V. Mechanisms of water and sodium retention in cirrhosis and the pathogenesis of ascites. *Best Pract Res Clin Endocrinol Metab* 2003;17:607–22.
6. Bosch J, Garcia-Pagan J. The splanchnic circulation in cirrhosis. In: Gines P, Arroyo V, Rhodes J, Schrier RW, eds. *Ascites and Renal Dysfunction in Liver Disease*, 2nd edition. Oxford, MA: Blackwell, 2005:156–63.
7. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med* 2006;199: S47–53.
8. Turner TB, Bennett VL, Hernandez H. The beneficial side of moderate alcohol use. *Johns Hopkins Med J* 1981;148:53–63.
9. Snowden C, Hughes T, Roberts DR. Pulmonary edema in patients after liver transplantation. *Liver Transplant* 2003;6: 466–70.
10. Donovan CL, Marcovitz PA, Punch JD, Back DS, Brown KA, Lucey MR, Armstrong WF. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation* 1996;61:1880–8.
11. Carey WD, Dumont JA, Pimentel RR, Barnes DS, Hobes RE, Henderson JM, Vogt DP, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation* 1995;59:859–64.
12. Plotkin JS, Scott VL, Pinna A, Dobsch BP, DeWolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996;2:426–30.
13. Morris JJ, Hellman CL, Gawey BJ, Ramsay MA, Valek TR, Gunning TC, Swygert TH, et al. Case 3-1995. Three patients requiring both coronary artery bypass surgery and orthotopic liver transplantation. *J Cardiothorac Vasc Anesth* 1995;9:322–32.
14. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, Flamm S, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. *Am J Cardiol* 2006;98:178–81.
15. United Network for Organ Sharing Organ Procurement. *The U.S. Transplant Network/Scientific Registry of Transplant Recipients 2006 Annual Report: Transplant Data*. Available at http://www.ustransplant.org/annual_reports/current/survival_rates.htm
16. Yang H, Raymer K, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. *Am Heart J* 2006;152:983–90.
17. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005;173:627–34.
18. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med* 1990;323:1781–8.
19. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2002;39:542–53.
20. Torregrosa M, Aguade S, Dos L, Segura R, Gonzalez A, Evangelista A, Castell J, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. *J Hepatol* 2005;42: 68–74.
21. Matsumori A. Hepatitis C virus infection and cardiomyopathies. *Circ Res* 2005;96:114–47.
22. Templin C, Pertschy S, Schaefer A. Cardiac hemochromatosis. *Int J Cardiol* 2007;117:e109–10.
23. Fealey ME, Edwards WD, Grogan M, Dispenzieri A. Primary cardiac amyloidosis with 20-year survival. *Cardiovasc Pathol* 2006;15:331–5.
24. Harley ID, Jones EF Liu G, McCall PR, McNicol PL. Orthotopic liver transplantation in two patients with hypertrophic obstructive cardiomyopathy. *Br J Anaesth* 1996;77:675–7.
25. Paramesh AS, Fairchild RB, Quinn TM, Leya F, George M, VanThiel DH. Amelioration of hypertrophic cardiomyopathy using nonsurgical septal ablation in a cirrhotic patient prior to liver transplantation. *Liver Transpl* 2005;11:236–8.
26. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 2006;43(Suppl 1):s121–31.
27. Valeriano V, Funaro S, Lionetti R, Riggio O, Pulcinelli G, Fiore P, Masini A, et al. Modification of cardiac function in cirrhotic patients with and without ascites. *Am J Gastroenterol* 2000;95:3200–5.
28. Ma Z, Lee SS. Cirrhotic cardiomyopathy: getting to the heart of the matter. *Hepatology* 1996;24:451–9.
29. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Belndis L. The cardiac response to exercise in cirrhosis. *Gut* 2001;49:288–75.
30. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. *Gastroenterol Clin Biol* 2002;26:842–7.
31. Bernardi M, Rubboli A, Trevisani F, Cancellieri C, Ligabue A, Baraldini M, Gasbarrini G, et al. Reduced cardiovascular responsiveness to exercise-induced sympathoadrenergic stimulation in patients with cirrhosis. *J Hepatol* 1991;12:207–16.
32. Grose RD, Nolan J, Dillon JF. Exercise-induced left ventricular dysfunction in alcoholic and nonalcoholic cirrhosis. *J Hepatol* 1995;22:326–32.
33. Milani A, Zaccaria R, Bombardieri G, Gasbarrini A, Pola P. Cirrhotic cardiomyopathy. *Dig Liver Dis* 2007;39:507–15.
34. Schwartz JM, Beymer C, Althaus SJ, Larson AM, Zaman A, Glickerman DJ, Kowdley KV, et al. Cardiopulmonary consequences of transjugular intrahepatic portosystemic shunts: role of increased pulmonary artery pressure. *J Clin Gastroenterol* 2004;38:590–4.
35. Henricksen JH, Fuglsang S, Bendtsen F, Christensen E, Moller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. *J Hepatol* 2002;36:513–20.
36. Roden DM, Viswanathan PC. Genetics of acquired long QT syndrome. *J Clin Invest* 2005;115:2025–32.