Internal and Emergency Medicine (2019) 14:907–910
https://doi.org/10.1007/s11739-019-02103-6

IM - COMMENTARY

The two congested failing giants: heart and liver

Piero Portincasa[1,2]

Received: 8 April 2019 / Accepted: 2 May 2019 / Published online: 11 May 2019

Liver disease related to the heart includes acute liver injury due to the heart, i.e., myocardial infarction, sustained arrhythmia resulting in passive congestion of the liver, chronic passive liver congestion, and "cardiac cirrhosis" [1]. Causes of congestive heart failure appear in Fig. 1 [1]. Congestive heart failure occurs when patients with advanced heart failure experience persistent and severe symptoms interfering with daily life. Advanced congestive heart failure manifests with typical symptoms (Fig. 1) and, by definition, manifestations occur despite maximum evidence-based medical therapy of heart failure, and reversible causes addressed [2, 3]. Advanced heart failure has major socio-economic burden; patients experience recurrent hospitalization, and the risk of mortality increases with the frequency of re-hospitalization [4, 5]. We reported that addressing an intensive outpatient management program to patients with chronic heart failure has beneficial long-term effects on clinical parameters, and decreases hospitalization [6].

Durante-Mangoni et al. [7] describe a retrospective study on clinical and histopathological features of liver injury in consecutive patients with advanced heart failure, seen between 2008 and 2016. The authors acknowledge that cardiogenic liver disease is a common, but yet poorly characterized complication of advanced congestive heart failure. Despite previous studies [8, 9], information about the ultimate impact of advanced heart failure in the liver shows a wide variability. The authors reviewed 228 inpatients undergoing screening for heart transplant. Forty-five patients underwent liver biopsy for suspected liver disease and median duration of cardiac symptoms of 5 years (class NYHA II–IV secondary to ischemic heart disease 31% and non-ischemic dilated cardiomyopathy 69%). Inclusion criteria were broad and included hepatomegaly, pruritus, jaundice and ascites, ultrasonographic findings of liver disease and portal hypertension, upper endoscopy positive for varices, and abnormally persistent liver function tests.

The liver receives about one-forth of cardiac output, is very prone to injury when conditions affect blood vessels, and contribute to passive congestion or decreased perfusion [10]. Patients developing right-sided heart failure alone or associated with left-sided heart failure may evolve to hepatic congestion, i.e., congestive hepatopathy resulting in elevation of central venous pressure. Congestive hepatopathy is suggested by liver enzyme abnormalities and right-sided heart failure or other cause of elevated central pressures. Three major pathogenetic mechanisms predispose to hepatic injury under conditions of congestion, i.e., decreased hepatic blood flow, decreased arterial oxygen saturation, and increased hepatic venous pressures (Fig. 1) [10]. At gross examination, the congestive liver has a "nutmeg" appearance [11] with dark centrilobular zones (sinusoidal congestion), which alternate with pale (normal) or yellowish (fatty) periportal zones [11, 12].

Durante-Mangoni et al. [7] found that patients had a stiff enlarged hepatomegaly, and elevated bilirubin. They also included 19 viral hepatitis patients (42%), often encountered in the "real-life" setting without an a priori exclusion criterion for heart transplant. Included were also patients with fatty liver, hemochromatosis, autoimmune liver disease, or alcohol intake > 40 g/day in men and 30 g/day in women. A complete cardiovascular functional assessment by echocardiography and Doppler ultrasound was performed.

Histological changes in congestive hepatopathy include sinusoidal dilatation and edema, hepatic cord atrophy, congestion, fatty change, red blood cells showing extravasation into the Disse space, especially with increasing hepatic venous pressure [13, 14]. Cholestasis can also occur and bile thrombi appear in the canaliculi [15]. Hepatic and right atrial pressures, and ischemia do show a correlation with the extent of inflammatory changes, necrosis (especially

✉ Piero Portincasa
piero.portincasa@uniba.it

[1] Division of Internal Medicine "Augusto Murri", Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro'', Bari, Italy

[2] Department of Biomedical Sciences and Human Oncology, Clinica Medica "Augusto Murri", University of Bari Medical School, Policlinico Hospital, Piazza Giulio Cesare 11, 70124 Bari, Italy

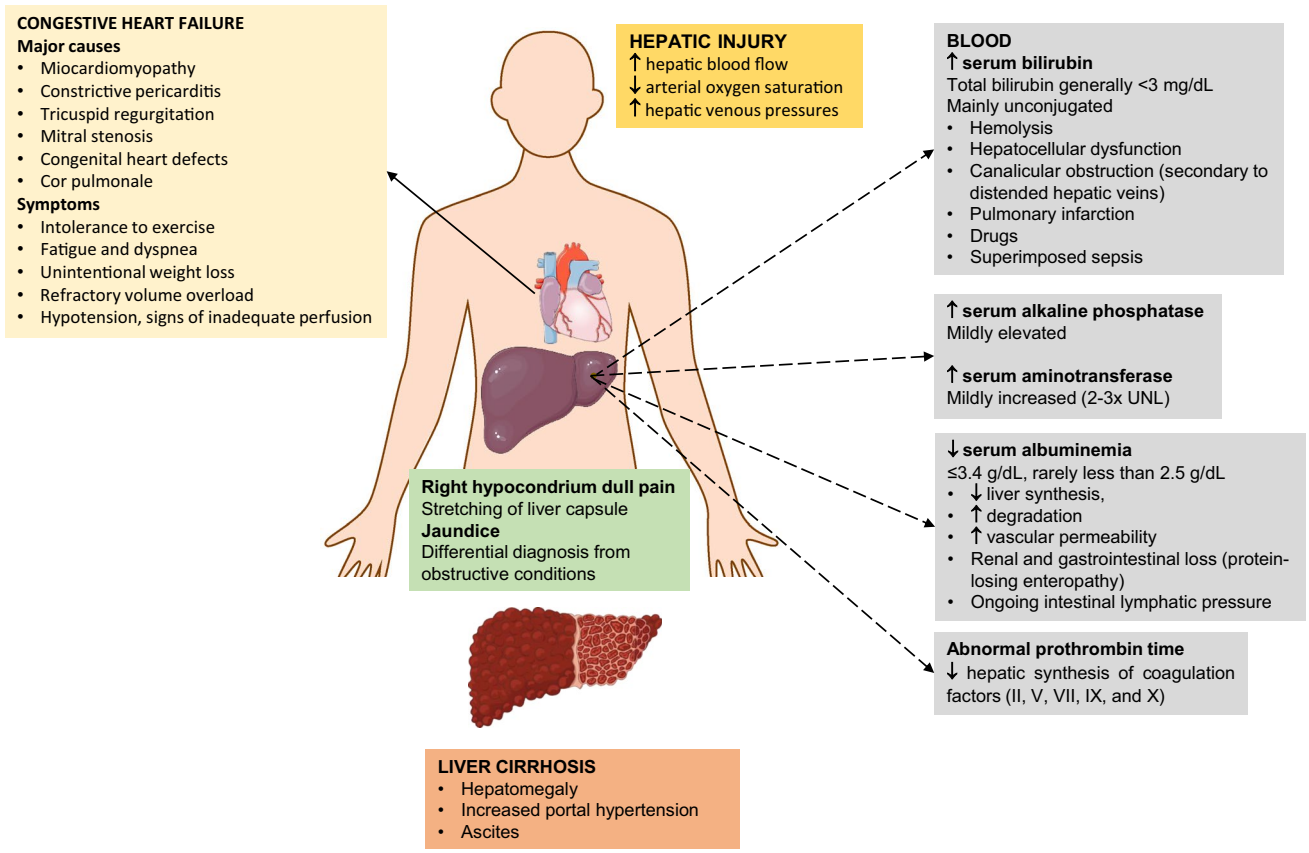

Fig. 1 Major etio-pathological, clinical, and laboratory changes with ongoing congestive heart failure and congestive hepatopathy. Causes of congestive heart failure and symptoms appear in the left upper yellow box. Major causes of hepatic injury, symptoms (pain), sign (jaundice), and blood abnormalities (ULN = upper normal limit) appear in the other boxes. In particular, hyperbilirubinemia [28] occurs in about 70% of the patients and correlates more with right atrial pressure than cardiac output [11]. Several factors contribute to elevated bilirubin [11], which is associated with increased risk of death in heart failure [28]. A subgroup of patients show increased serum aminotransferase levels [17] from ongoing ischemic hepatitis due to defective cardiac output [29]. Hypoalbuminemia occurs in 30% to 50% of the patients with advanced heart failure, and is associated with worse prognosis [30, 31]. Few factors contribute to this finding [32, 33]. Longstanding right heart failure and elevated central venous pressure can also evolve to liver cirrhosis [14], and symptoms include a dull pain in the right hypocondrium because of stretching of the liver capsule. Jaundice requires differential diagnosis from obstructive conditions. Liver cirrhosis will be associated with increasing portal hypertension [34] and hepatomegaly, more evident signs of right-heart failure, hepatojugular reflux and peripheral edema. If tricuspid regurgitation develops, the liver might become pulsatile, a sign which is loss with ongoing liver fibrosis and cirrhosis [33]. With ascites, the diagnostic paracentesis shows high total protein content (> 2.5 g/dL, due to preserved synthetic function of the liver [10]) (colour figure online)

in zone 3) [16] and dilatation [9]. Liver cirrhosis is secondary to the ongoing process of perivenular fibrosis with accumulation of reticulin and collagen in zone 3, due to the chronic congestive status. Tipically, the fibrous bands extend outward from the central veins. The fibrous tissue can link with portal tracts (namely cardiac fibrosis) with a picture resembling the micronodular cirrhosis. The ongoing portal fibrosis during congestive hepatopathy relates to increased right atrial pressure, as well as dilatation of the right atrium and ventriculum [14].

Durante-Mangoni et al. [7] looked at necroinflammatory histological activity index, fibrosis by the Ishak scoring system, and steatosis. Sinusoidal dilatation occurred in 64% of the patients, irrespective of heart disease aetiology or severity. Median necroinflammatory index was 3, median fibrosis was 1, and steatosis was absent. The picture is a minor burden of histologically-proven liver disease. Viral hepatitis was the only variable associated with a higher grade of necroinflammation and advanced fibrosis/cirrhosis. A viral hepatitis infection was found in 64% of the subgroup of patients ($N = 14$) with advanced fibrosis/cirrhosis. Splenomegaly was significantly associated with fibrosis. In addition, levels of liver injury markers, the histology activity index, fibrosis and steatosis were similar in patients with ischemic and non-ischemic cardiomyopathy, and according cardiac functional parameters. The Model for End-Stage Liver Disease (MELD) score did not correlate with cardiac index. A poor correlation

existed between histologic and ultrasonographic parameters. By ultrasonography, a coarse pattern had a 29% positive and 63% negative predictive value for advanced fibrosis/cirrhosis.

Several patients with congestive hepatopathy will not diplay liver disease. With increased hepatic congestion, however, abnormal liver biochemical tests and symptoms develop (Fig. 1). The therapy of congestive hepatopathy must focus on the underlying heart disease with optimization of cardiac output, to slow down the ongoing changes due to liver congestion. Diuretics require attention due to potential deterioration of hepatic ischemia [17]. The procedure of left ventricular assist device (LVAD) implantation or cardiac transplantation are reserved to patients unresponsive to maximal medical management and fulfilling the inclusion criteria [18, 19]. MELD and modified MELD will identify patients with worse outcomes one month after surgery and reduced survival rates after 10 years [20]. Overall, congestive hepatopathy is not associated with significant morbidity or mortality or poorer prognosis, which instead depends on the underlying heart disease. Thus, the optimization of cardiac function may positively affect the natural history of cardiac cirrhosis. A sudden ischemic hit (i.e., a superimposed shock), however, might explain a picture of fulminant hepatic failure [21].

Durante-Mangoni et al. [7] conclude that severe liver disease ("cardiac cirrhosis") is uncommon in patients with advanced heart failure. Other causes of liver disease may exist if clinical, biochemical or ultrasonographic features suggest severe liver disease in the subgroup of patients with concomitant viral hepatitis, alcohol abuse or splenomegaly. Further comments are that ultrasonography may overstate the severity of liver disease, unless other causes of liver disease exist, and the echo-pattern is influenced by prolonged liver congestion and impaired perfusion during heart failure. The role of liver stiffness also requires attention. The Fibrosis-4 (FIB4) index, a marker of liver stiffness (age [years] × aspartate aminotransferase [IU/L]/platelet count [10^9/L] × $\sqrt{}$ alanine aminotransferase [IU/L]), is associated with higher all-cause mortality in patients with heart failure [22]. In acute decompensated heart failure, liver stiffness by elastography shows high values (media 8.8 kPa) decreasing with clinical improvement [23]. Guidelines underscore that by elastography, comorbidities such as acute, chronic liver disease, heart failure, congestive heart failure, and extrahepatic cholestasis, represent sources of variability [24]. Magnetic resonance imaging (MRI) might also play a role in the diagnosis of hepatic congestion and edema, irregular postgadolinium hepatic enhancement on multiple phases. The presence of irreversible chronic liver disease and hepatic fibrosis will result in enhancement with a fine reticular and coarse linear pattern that develops progressively on venous and delayed phase images [25].

Despite potential bias due to sampling error [26, 27] liver biopsy will accurately stage liver disease, advanced fibrosis, B and C viral infection (which currently can be cured or suppressed effectively). This step has a role before excluding patients from advanced treatment strategies (i.e., heart transplant or implant a mechanical circulatory support device), and acknowledges guidelines of the International Society for Heart Lung Transplantation [3].

Compliance with ethical standards

Conflict of interest The authors certify that they have no affiliation or financial involvement in any organization with a direct financial interest in the subject matter discussed in the manuscript.

Statement of human and animal rights All procedures performed in studies discussed in the manuscript were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of paper (commentary) formal consent is not required.

References

1. Ford RM, Book W, Spivey JR (2015) Liver disease related to the heart. Transplant Rev 29(1):33–37 **(Orlando)**
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL (2013) 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 128(16):1810–1852
3. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A, International Society for Heart Lung Transplantation Infectious Diseases C, International Society for Heart Lung Transplantation Pediatric Transplantation C, International Society for Heart Lung Transplantation Heart F, Transplantation C (2016) The 2016 international society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transpl 35(1):1–23
4. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA, Candesartan in Heart failure: Assessment of Reduction in M, morbidity I (2007) Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 116(13):1482–1487
5. Setoguchi S, Stevenson LW, Schneeweiss S (2007) Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 154(2):260–266
6. Belfiore A, Palmieri VO, Di Gennaro C, Settimo E, De Sario MG, Lattanzio S, Fanelli M, Portincasa P (2019) Long-term

management of chronic heart failure patients in internal medicine. Intern Emerg Med. https://doi.org/10.1007/s11739-019-02024-4
7. Durante-Mangoni E, Parrella A, Pafundi PC, Vitrone M, Ragone E, De Rosa I, Amarelli C, Zampino R (2019) Liver histopathological findings in advanced heart failure: a reappraisal of cardiac cirrhosis concept. Intern Emerg Med. https://doi.org/10.1007/s11739-019-02033-3
8. Gelow JM, Desai AS, Hochberg CP, Glickman JN, Givertz MM, Fang JC (2010) Clinical predictors of hepatic fibrosis in chronic advanced heart failure. Circ Heart Fail 3(1):59–64
9. Myers RP, Cerini R, Sayegh R, Moreau R, Degott C, Lebrec D, Lee SS (2003) Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology 37(2):393–400
10. Hilscher M, Sanchez W (2016) Congestive hepatopathy. Clin Liver Dis 8(3):68–71
11. Sherlock S (1951) The liver in heart failure; relation of anatomical, functional, and circulatory changes. Br Heart J 13(3):273–293
12. Lefkowitch JH, Mendez L (1986) Morphologic features of hepatic injury in cardiac disease and shock. J Hepatol 2(3):313–327
13. Arcidi JM Jr, Moore GW, Hutchins G (1981) Hepatic morphology in cardiac dysfunction: a clinicopathologic study of 1000 subjects at autopsy. Am J Pathol 104(2):159
14. Dai DF, Swanson PE, Krieger EV, Liou IW, Carithers RL, Yeh MM (2014) Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. Mod Pathol 27(12):1552–1558
15. Koehne de Gonzalez AK, Lefkowitch JH (2017) Heart disease and the liver: pathologic evaluation. Gastroenterol Clin N Am 46(2):421–435
16. Bynum TE, Boitnott JK, Maddrey WC (1979) Ischemic hepatitis. Dig Dis Sci 24(2):129–135
17. Weisberg IS, Jacobson IM (2011) Cardiovascular diseases and the liver. Clin Liver Dis 15(1):1–20
18. Russell SD, Rogers JG, Milano CA, Dyke DB, Pagani FD, Aranda JM, Klodell CT Jr, Boyle AJ, John R, Chen L, Massey HT, Farrar DJ, Conte JV, HeartMate IICI (2009) Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation 120(23):2352–2357
19. Dichtl W, Vogel W, Dunst KM, Grander W, Alber HF, Frick M, Antretter H, Laufer G, Pachinger O, Polzl G (2005) Cardiac hepatopathy before and after heart transplantation. Transpl Int 18(6):697–702
20. Chokshi A, Cheema FH, Schaefle KJ, Jiang J, Collado E, Shahzad K, Khawaja T, Farr M, Takayama H, Naka Y, Mancini DM, Schulze PC (2012) Hepatic dysfunction and survival after orthotopic heart transplantation: application of the MELD scoring system for outcome prediction. J Heart Lung Transpl 31(6):591–600
21. Kisloff B, Schaffer G (1976) Fulminant hepatic failure secondary to congestive heart failure. Am J Dig Dis 21(10):895–900
22. Sato Y, Yoshihisa A, Kanno Y, Watanabe S, Yokokawa T, Abe S, Misaka T, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Saitoh SI, Takeishi Y (2017) Liver stiffness assessed by fibrosis-4 index predicts mortality in patients with heart failure. Open Heart 4(1):e000598
23. Colli A, Pozzoni P, Berzuini A, Gerosa A, Canovi C, Molteni EE, Barbarini M, Bonino F, Prati D (2010) Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. Radiology 257(3):872–878
24. Barr RG, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J, Garra B, Myers RP, Wilson SR, Rubens D, Levine D (2015) Elastography assessment of liver fibrosis: society of radiologists in ultrasound consensus conference statement. Radiology 276(3):845–861
25. Chundru S, Kalb B, Arif-Tiwari H, Sharma P, Costello J, Martin DR (2013) MRI of diffuse liver disease: the common and uncommon etiologies. Diagn Interv Radiol 19(6):479–487
26. Persico M, Palmentieri B, Vecchione R, Torella R (2002) Diagnosis of chronic liver disease: reproducibility and validation of liver biopsy. Am J Gastroenterol 97(2):491–492
27. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng ZZ, Reddy KR, Schiff ER (2002) Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 97(10):2614–2618
28. Allen LA, Felker GM, Pocock S, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB, Investigators C (2009) Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) program. Eur J Heart Fail 11(2):170–177
29. Cohen JA, Kaplan MM (1978) Left-sided heart failure presenting as hepatitis. Gastroenterology 74(3):583–587
30. Uthamalingam S, Kandala J, Daley M, Patvardhan E, Capodilupo R, Moore SA, Januzzi JL Jr (2010) Serum albumin and mortality in acutely decompensated heart failure. Am Heart J 160(6):1149–1155
31. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC (2008) Albumin levels predict survival in patients with systolic heart failure. Am Heart J 155(5):883–889
32. Arques S, Ambrosi P (2011) Human serum albumin in the clinical syndrome of heart failure. J Card Fail 17(6):451–458
33. Giallourakis CC, Rosenberg PM, Friedman LS (2002) The liver in heart failure. Clin Liver Dis 6(4):947–967
34. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yeshurun D (2000) Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 140(1):111–120