Acute-on-chronic liver failure: the heart and systemic hemodynamics
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Purpose of review
Circulatory abnormalities in cirrhosis include hyperdynamic circulation and cirrhotic cardiomyopathy. The extent of circulatory abnormalities is further exaggerated in acute-on-chronic liver failure (ACLF). The mechanism remains unclear and management also needs to be evaluated.

Recent findings
The predominant mechanism of ACLF is thought to be a systemic inflammatory reaction. Cardiovascular-active factors such as tumor necrosis factor and nitric oxide are increased and cortisol is decreased; the former further dilates the vasculature and the latter decreases the sensitivity to vasoconstrictors. The exaggerated vasodilatation further decreases the cardiac afterload. However, no study has yet demonstrated the benefit of vasodilators/vasoconstrictors in the management of ACLF. Standard medical treatment in this setting is associated with high mortality. Patients treated with molecular adsorbent recirculating system (MARS) had improved serum levels of inflammatory mediators such as tumor necrosis factor alpha and interleukin-6, but this was not associated with improved survival. Liver transplantation eventually reverses the cardiovascular abnormalities.

Summary
Circulatory abnormalities are exaggerated in ACLF. The predominant mechanism is a systemic inflammatory reaction. Modalities such as MARS improve serum markers of inflammation, but not survival. Liver transplantation is the definitive treatment of the cardiovascular abnormalities of ACLF.

Keywords
acute-on-chronic liver failure, cirrhotic cardiomyopathy, hyperdynamic circulation, molecular adsorbent recirculating system

Introduction
In patients with chronic or acute-on-chronic liver failure (ACLF), the circulation becomes abnormal. The two dominant abnormalities are the peripheral vasculature which undergoes a phenomenon termed 'hyperdynamic circulation' (HDC), and the heart, which is affected by 'cirrhotic cardiomyopathy' (CCM). HDC manifests as increased cardiac output (CO) and decreased peripheral vascular resistance and arterial pressure. This type of hyperkinetic circulation is found in virtually all regional vascular beds examined to date including the hepatomesenteric (splanchnic), renal, pulmonary, and skeletal muscle. Whether it affects the privileged brain/central nervous system circulation remains unclear. In the biggest regional bed, the splanchnic, the increased blood flow exacerbates the portal hypertension and thus increases the risk of variceal bleeding. HDC also is a major factor in the pathogenesis of the other major complication of portal hypertension, ascites. Currently, the leading theory of ascites formation is the 'peripheral vasodilatation' hypothesis, which states that the massive vasodilatation induces an increased effective circulating volume that is sensed by the kidney as overt hypovolemia, leading to salt and water retention.

Hyperdynamic circulation
ACLF is defined as the acute deterioration of liver function over a period of 2–4 weeks, usually associated with a precipitating event, in a patient with previously well compensated chronic liver disease. The predominant mechanism of ACLF is thought to be a systemic inflammatory reaction that leads to severe deterioration in clinical status, with jaundice and hepatic encephalopathy, ascites, or hepatorenal syndrome (HRS). Many
Clinical manifestations of chronic liver failure are aggravated in ACLF, including HDC. Kumar et al. [1] studied portal, systemic, and pulmonary hemodynamics in patients with ACLF and compared them with compensated and decompensated cirrhotics. They found that the mean arterial pressure (MAP) and systemic vascular resistance (SVR) were lower in the ACLF group than in the compensated group and similar to that in the decompensated group. Similarly, the mean CO of the ACLF patients was higher than that in the compensated group and similar to that in the decompensated group.

The mechanism of the further exaggerated HDC in ACLF remains unclear. Most authorities believe that the further increase in HDC arises from an aggravation of the same mechanism underlying IIDC in chronic liver failure, namely an imbalance of vasodilator and vasoconstrictor influences. According to this concept, vasodilation is due to a reduction in vascular responsiveness by downregulation of receptors, leading to hyposensitivity to vasoconstrictors. There may also be overactivity or overexpression of vasodilators such as nitric oxide. However, we believe that this strictly ‘peripheral’ or end-organ pathogenesis is an oversimplification. Over the past decade, our laboratory has demonstrated in rat models of portal hypertension and cirrhosis that central neural activation in the brainstem and hypothalamic cardiovascular-regulatory nuclei such as the nucleus of the solitary tract, is a sine qua non for the development of HDC in portal hypertension [2–5]. Whether further central neural dysregulation also plays a role in the aggravation of HDC in ACLF remains unstudied to date.

Whatever the mechanism of HDC, it is undeniable that a significant acute inflammatory reaction exists in ACLF. Inflammation per se may induce circulatory dysfunction, even HDC. One need only consider the ‘warm phase’ of septic shock as an example – CO increases and peripheral vascular resistance markedly diminishes. It is reasonable to consider therefore that inflammation via mechanisms that remain incompletely elucidated thereby increases the magnitude of HDC in ACLF.

**Relative adrenal insufficiency**

Relative adrenal insufficiency in patients with severe sepsis is recognized [6]. ACLF patients also have significant endotoxemia which activates neutrophils [7••]. Accordingly, features of the sepsis syndrome are likely to be even more marked compared with CLF alone. Thus, ACLF is expected to be associated with relative adrenal insufficiency. Aravinthan et al. [8•] reported that in a patient with variceal bleeding (Aclf) despite adequate vascular filling and no evidence of ongoing bleeding, he remained persistently hypotensive, necessitating the addition of noradrenaline to maintain blood pressure. A short synacthen test (SST) demonstrated a blunted response signifying severe adrenocortical insufficiency. After intravenous hydrocortisone administration, the patient recovered the response to noradrenaline. In a prospective study, Fernandez et al. [9] found that the incidence of adrenal insufficiency in patients with cirrhosis and septic shock was 68%.

Cortisol has several beneficial effects in ACLF. First, it is a powerful immunosuppressive hormone and reduces the inflammatory response and cytokine production. By this mechanism, it inhibits the production of nitric oxide and other mediators of septic shock [10]. A direct inhibitory effect of cortisol on the inducible form of nitric oxide synthase has also been demonstrated [11]. Second, cortisol is important in the maintenance of vascular tone and permeability and third, it increases the vascular and cardiac response to the renin–angiotensin and the sympathetic nervous systems. The study of Aravinthan et al. [8•,12] showed that after the patient recovered from the acute insult, the subsequent investigations for adrenal disorders including pituitary MRI scan, adrenal computed tomography, and adrenal autoantibodies were all normal. All of these results therefore suggested that it was the acute event that triggered the relative adrenal insufficiency.

**Increased vasodilator influences**

Cytokines are believed to play an important role in ACLF. Elevated serum levels of several cytokines, including tumor necrosis factor alpha (TNFα), was observed in portal vein hypertensive rats [13]. Using anti-TNF-α antibody to neutralize the increased TNFα significantly decreased cardiac index and portal vein pressure and increased MAP and SVR, that is, it reversed the HDC in a portal hypertensive animal model. TNFα and soluble TNFα receptor-1 are significantly elevated in patients with ACLF [14], and this was associated with increased magnitude of HDC. The plasma TNFα level in ACLF patients treated with the molecular adsorbent recirculating system (MARS) was significantly decreased compared with that in ACLF patients treated with standard medical therapy [15••]. The extent of HDC was significantly improved after MARS treatment; but again, this observation is circumstantial, not confirmatory evidence of a relationship between cytokines and HDC in ACLF.
Another direct vasodilator is nitric oxide. Nitric oxide plays an important role in HDC in cirrhosis, although whether it is truly causal or merely an associational relationship remains still to be completely clarified. What is the role of nitric oxide in ACLF? Jalan et al. [7**] investigated cirrhotic patients with transjugular intrahepatic stent-shunt (TIPSS) insertion and found that this procedure results in a further increase in CO and a reduction in SVR. Nitric oxide may play a role in mediating the HDC of cirrhosis and splanchnic vasodilatation as evidenced by the ability of specific nitric oxide synthase inhibitors to correct vascular hyporesponsiveness in vitro and in vivo [16,17]. In patients with cirrhosis, inhibition of nitric oxide synthase results in a reduction in CO and an increase in SVR and MAP [18]. These cardiovascular changes may result in an increase in shear stress, which activates endothelial nitric oxide (eNOS) synthase and, therefore, nitric oxide production [19,20]. The study of Jalan et al. suggests that this increase in nitric oxide production may be the result of endotoxemia and is mediated by inducible nitric oxide synthase (iNOS). However, the current nitric oxide hypothesis about the mechanism of systemic vasodilatation in cirrhosis is thought to be eNOS-driven. Their explanation is that the TIPSS-superimposed inflammatory insult reverts to being primarily iNOS driven.

There is also ample evidence for a role for the third NOS isoform, nNOS. Mice with both iNOS and eNOS genes 'knocked out' still develop HDC after portal vein ligation [21]. Xu et al. [22] showed a selective nNOS inhibitor abrogated HDC in rats with CCl4-induced cirrhosis. Several other lines of evidence also support a role of nNOS in the genesis of HDC in animal models of cirrhosis/portal hypertensions [23,24].

**Increased intrahepatic resistance**

The increased vasodilator influence further triggers abnormal distribution of the plasma volume with hyperemia in the splanchnic region (splanchnic hyperanemia) and 'effective hypovolemia' in the systemic circulation. This leads to activation of endogenous vasoconstrictors and water-retaining and sodium-retaining systems such as the renin–angiotensin–aldosterone system and the sympathetic nervous system, and in the nonsomotic release of arginine vasopressin. Persistent activation of these systems appears to worsen the increased intrahepatic resistance. It was demonstrated that nitric oxide is significantly increased in the systemic circulation and decreased in the intrahepatic circulation [16]. The imbalance of vasodilators/vasoconstrictors thus plays a key role in the aggravation of portal hypertension [25]. Several studies have emphasized the relation between the degree of arterial hypotension in cirrhosis and the severity of portal hypertension, hepatic dysfunction, signs of decompensation, and survival [26–28].

**Cirrhotic cardiomyopathy**

The heart responds abnormally to numerous stimuli/stresses. Cardiac ventricular function under physiological, pharmacological, or surgical stress is blunted, with abnormalities of both systolic and diastolic function. This condition is known as CCM. Other features of the syndrome include electrophysiological changes in repolarization including prolonged electrocardiographic QT interval, enlargement or hypertrophy of cardiac chambers, and markers of cardiac 'distress' such as BNP or pro-BNP and troponin I.

Although some of these cardiac changes when initially described almost four decades ago were ascribed to a mild or latent form of alcoholic cardiotoxicity, it is now incontrovertibly established that the condition of cirrhosis per se is associated with this, as patients and animal models with nonalcoholic cirrhosis show the same pattern of cardiac dysfunction. Recent evidence implicates a significant pathogenic role of this syndrome in the development of acute HRS and poor outcomes such as increased mortality/morbidity after challenges such as TIPS insertion and liver transplantation. It may also explain the uncommon but mysterious and inexplicable onset of heart failure in the peri-transplantation and post-transplantation period in patients with no previous history of heart disease or dysfunction.

Whether CCM worsens during ACLF compared with CLF remains unstudied. The study of patients with resolving spontaneous bacterial peritonitis (SBP) who developed HRS, by Ruiz-del-Arbol et al. [29] is interesting. Eight of 23 patients admitted with SBP developed HRS after infection resolution. Compared with the 15 renal-unimpaired patients, the HRS group had a lower CO at admission, and this declined further after infection resolution, whereas CO remained unchanged in the former group. We speculated that the infection or inflammatory insult during the period of SBP (and thus a prime example of ACLF) somehow further aggravated the extent of ventricular dysfunction and thus helped trigger the onset of HRS [30].

Several pathogenic mechanisms of CCM have been described including dysfunction or defects in the cardiac β-adrenergic receptor system, plasma membrane physicochemical milieu, membrane calcium channels, and humoral factors such as cytokines, nitric oxide, carbon monoxide, and endogenous cannabinoids. Extensive discussion of these putative mechanisms is beyond the scope of this review; recent reviews may be consulted [5,31–33]. Many of these pathogenic mechanisms are
interrelated and their exact relationship is the subject of ongoing research.

Management
Appropriate management strategies for the cardiovascular anomalies associated with ACLF remain unclear. The patient’s overall cardiovascular status must be considered and managed, not just a single problem in isolation such as CCM, HDC, or hepatopulmonary syndrome. Sometimes, the treatment for one condition may exacerbate the other. For example, attempts to decrease the extent of HDC by vasoconstrictor therapy may potentially worsen the cardiac function. Indeed, some evidence suggests that a major reason why CCM remains subclinical in many patients is that significant peripheral vasodilatation ‘unloads’ the ventricle and thus autotreats the heart problem. Recommending treatment approaches is difficult due to the lack of well designed controlled trials examining different management strategies, especially for CCM, but also for HDC to a lesser extent.

However, some general principles can be applied. HDC per se need not be treated, that is, treatments to decrease overall systemic vasodilatation are probably not necessary. Treatment should be initially directed to the vascular bed causing the greatest clinical problem, with the hope that the treatment will not exacerbate other cardiovascular variables. For example, systemic vasoconstrictor therapy with terlipressin is justified for HRS, even though it may potentially decrease CO.

Treatment strategies for CCM remain unclear. Fortunately, overt heart failure is distinctly uncommon. Repolarization abnormalities such as QT prolongation may respond to β-blockade [34]. Promising avenues of inquiry include cardiac antifibrogenic therapies such as angiotensin-converting enzyme inhibitors, but these will not be applicable to the ICU setting. If overt heart failure is present, the standard measures including further afterload reduction can be considered.

Standard medical therapy and new approaches
Standard medical therapy such as antibiotics for SBP or infection, blood replacement for bleeding, lactulose, and antibiotics for encephalopathy are well known and do not need repeating here. ACLF shows a high mortality rate with standard therapy, so new approaches are under study. Novelli et al. [15**] reported that 70% of their patients died within 3 months in the standard therapy group.

MARS is under investigation since standard treatments for ACLF are so dismal [25]. Laleman et al. demonstrated that MARS improves hemodynamic disturbances in patients with ACLF with associated HDC. They showed that MARS therapy compared with standard medical therapy did not change the fluid balance, serum albumin, or creatinine levels. These beneficial hemodynamic effects can be explained by the removal of circulating endogenous vasoactive substances [35]. This favorable effect on the MAP in patients treated with MARS disappeared within 4 days after cessation of treatment.

MARS may improve HDC in ACLF patients via three mechanisms: first, it decreases nitric oxide levels. Laleman et al. found that the reduction of nitric oxide levels was negatively correlated with the improvement of SVR. Second, MARS might decrease the intrahepatic action of vasoconstrictors [35,36], such as vasopressor hormones, norepinephrine, and aldosterone. Third, it can remove inflammatory mediators such as TNFα. Some studies demonstrated that anti-TNFα antibody attenuates portal hypertension and the associated hyperdynamic state, both experimentally [13] and in humans [37].

The major issue however with MARS is the current failure to demonstrate a clear survival advantage despite all the improvements in circulatory and biomarker indices. Thus, further study is needed before any conclusions can be drawn regarding this experimental mode of therapy.

Liver transplantation
Liver transplantation is the only therapeutic option for patients with end-stage liver diseases. It is also one of the best options for the treatment of ACLF. It has been demonstrated that liver transplantation eventually normalizes HDC in cirrhotic patients [38]. However, to date, there has been no study of the circulation changes after liver transplantation in patients with ACLF. Siniscalchi et al. [39] investigated the circulatory changes in acute liver failure treated with liver transplantation and demonstrated that in 24h after surgery, 41% of the patients significantly decreased systemic blood pressure, SVR, CO, and moderately increased pulmonary arterial pressure. These circulatory changes were speculative due to the increases in pro-inflammatory cytokines, such as interleukin-6 or TNFα. Neutralization of these cytokines might be a potential avenue to alleviate circulatory dysfunction in ACLF.

Conclusion
Circulatory abnormalities are further exaggerated in ACLF. The predominant mechanism is a systemic inflammatory reaction. Imbalance of vasoconstrictor vs. vasodilator influences such as TNF, IL-6, nitric oxide, and cortisol may be involved in the pathogenesis of circulatory disorders in ACLF. The mortality with standard medical treatment is high. MARS improves HDC in
A CLF, but no firm survival advantage has been shown. Liver transplantation eventually reverses the cardiovascular anomalies.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 209).


Circulatory failure in A CLF is IONOS dependent.


•• Adrenal insufficiency in patients with A CLF causes the de-sensitivity of the vasculature to vasoconstrictors.


MARS liver support device reverts levels of cytokines, such as IL-6, IL-1, IL-10, TNFe toward normal.


