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Cardiac dysfunction in cirrhosis

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Cirrhosis is known to be associated with numerous cardiovascular abnormalities. These include increased cardiac output and decreased arterial pressure and total peripheral resistance. Despite this increased baseline cardiac output, patients with cirrhosis show an attenuated systolic and diastolic function in the face of pharmacological, physiological and surgical stresses, as well as cardiac electrical abnormalities such as QT prolongation. These abnormalities have been termed cirrhotic cardiomyopathy. The pathogenic mechanisms that underlie this syndrome include impairment of the β-adrenergic receptor signalling, cardiomyocyte plasma membrane function, intracellular calcium kinetics, and humoral factors such as endogenous cannabinoids, nitric oxide and carbon monoxide. Cirrhotic cardiomyopathy is believed to contribute to the cardiac dysfunction that can be observed in patients with transjugular intrahepatic portosystemic stent-shunt insertion and liver transplantation. Insufficient cardiac contractile function may also play a role in the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis. In this review, the clinical features, pathogenic mechanisms, clinical consequences and management options for cirrhotic cardiomyopathy are discussed.

Key words: cirrhotic cardiomyopathy; cirrhosis; cardiac; ventricular; heart failure; β-adrenergic; membrane fluidity; nitric oxide; endocannabinoid; carbon monoxide; QT interval.

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INTRODUCTION

That cirrhosis is associated with cardiovascular abnormalities has been part of clinical lore for centuries, but only until relatively recently did the development of techniques for precisely measuring cardiovascular variables allow determination of the extent of these anomalies. Before then, clinicians observed the tachycardia and bounding pulses of patients with cirrhosis and surmised that the circulation was hyperdynamic. In 1953 a seminal study by Kowalski and Abelmann determined that patients with alcoholic cirrhosis do indeed have increased cardiac output and decreased arterial pressure and total peripheral resistance, i.e., hyperdynamic circulation.[1] As for the heart, it was assumed that since basal cardiac output is increased, contractile function should, intuitively, be normal as well. Cardiac output is the product of heart rate and the volume of blood expelled with each contraction, or stroke volume (SV). Blood pressure is calculated by multiplying cardiac output by the total peripheral resistance. By this logic, then, an increase in vascular resistance should therefore be able to correct the hypotension secondary to hyperdynamic circulation. However, beginning in the late 1960s, evidence arose that showed this was not the case. Regan et al studied ten alcoholics with no clinical evidence of cardiac disease, along with eight healthy controls, and intravenously infused both groups with angiotensin. Angiotensin is an eight-amino acid oligopeptide which is produced in the body as part of the renin-angiotensin-aldosterone system. Among other roles, it acts on receptors in vascular tissue causing systemic arteriolar vasoconstriction, leading to increased vascular resistance and thereby elevating cardiac afterload. After angiotensin infusion, it was observed that although the left ventricular end diastolic pressure of the alcoholic group increased significantly more than the control group, the corresponding rise in stroke output and work was significantly less than the controls. This suggested a significantly attenuated ventricular contractile response to diastolic filling. At the time, however, this was merely attributed to the chronic effects of alcohol toxicity on the myocardium.[2] A similar result was noted shortly afterwards by Gould et al, who examined the cardiac response to exercise of ten male subjects with evidence of chronic liver disease. At rest, increases in stroke index and cardiac output of all participants were observed. With exercise, however, stroke index declined despite elevations in left ventricular end diastolic pressure, which represents a highly abnormal cardiac response.[3] Approximately five years later, Limas et al also infused angiotensin into ten patients with alcoholic cirrhosis, with no resultant increase in cardiac output. Subsequent administration of the cardiac glycoside ouabain yielded no rise in cardiac output.[4] Under normal conditions, glycosides should increase intracellular calcium through sodium–calcium exchange mechanisms, promoting contractility. This blunted cardiac response to both pharmacological and physiological stress was observed in several studies over the next decade and was always attributed to mild or latent alcohol-induced cardiomyopathy. It was not until 1986 when Caramelo and colleagues infused saline into rats with carbon tetrachloride-induced cirrhosis and noted a 50% decrease in their cardiac output, despite a 112% increase in total peripheral resistance. This landmark study indicated that the impaired cardiac contractile response was associated with cirrhosis *per se*, rather than a direct, adverse effect of alcohol.[5] This has since been confirmed by many studies in both humans and experimental animal models.[6–12] In 1989, this phenomenon was labelled as 'cirrhotic cardiomyopathy'.[6] In summation, it represents a syndrome in cirrhotic patients where cardiac output and contractility are normal or increased at rest, but abnormal in the presence of physiologic, pharmacologic or surgical stresses.