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Bile acids induce arrhythmias: old metabolite, new tricks

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Bile acids (BAs) have traditionally been viewed as mere 'detergent' molecules responsible for absorption of dietary fats and lipid-soluble vitamins. However, over the past decade, research in the field of bile acid biology has provided evidence which redefine BAs as potent circulating signalling molecules with the ability to regulate cell biology, metabolism and function of various extrahepatic organs,[1] with potential effects on the heart. BAs are secreted in the duodenum and then reabsorbed efficiently from the ileum back to the liver via mesenteric and portal veins. This tightly regulated enterohepatic circulation is disrupted in diseases of the liver such as obstructive jaundice, intrahepatic cholestasis of pregnancy, chronic viral hepatitis and cirrhosis, which leads to spillage of these metabolites into the systemic circulation at pathologically high concentrations (>100–200 μmol/L), resulting in organ dysfunction.[2, 3]

It has long been known that high levels of bile acids are toxic to the heart. The cardiotoxicity of bile acids was documented as early as 1863, by Röhrig, who showed that filtered ox bile when injected into the jugular veins of rabbits caused bradycardia, while repeated doses caused cardiac arrest, a phenomenon he described as 'cardiac paralysis'. At the same time, Landois showed that bile induced bradycardia persisted despite denervation of the heart and proposed a direct cardiodepressant effect of bile on the heart.[4] Wakim *et al*[5] in 1939 followed these observations by demonstrating that whole bile as well as sodium taurocholate salt produced hypotension, bradycardia and rhythm disturbance in dogs in the absence as well as the presence of cardiac autonomic nerves. Joubert in 1978 showed that infusion of cholic acid (primary unconjugated bile acid in humans) induced dose-dependent bradycardia in a rodent heart.[6, 7] In the late 1980s, Binah *et al*[8] were the first to report that taurocholic acid (TCA; conjugated primary bile acid) reduced slow inward Na^+ and Ca^{2+} current while increasing the outward K^+ current, thus reducing the duration of action potential in the ventricular myocytes. TCA has been associated with fetal arrhythmias, fetal stress and intrauterine deaths in intrahepatic cholestasis of pregnancy, and its arrhythmogenic properties have been extensively studied in rodent models by Gorelik and Williamson over the past decade.[9–11] However, whether TCA and other bile acids induce electrocardiographic abnormalities in adult hearts was unknown, and was the main focus of the current study.

Rainer *et al* describe a series of elegant experiments to support their hypothesis that hydrophobic conjugated bile acid at high concentrations induce arrhythmias in humans. Using isolated human atrial trabeculae, the authors demonstrate that TCA has a dose-

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dependent increase in arrhythmic extra contractions, without affecting key functional parameters of the heart such as contractile force, diastolic tension and relaxation. They further show that hydrophilic bile acid ursodeoxycholic acid (UDCA) and its taurine conjugate do not induce arrhythmias even at high concentrations.[12] These human experiments, which were faithfully reproduced in isolated adult mouse cardiomyocytes, further strengthen the long-held notion that high levels of circulating bile acids adversely affect myocardial cell biology. More importantly, these studies add clinical relevance to the animal studies which speculated a role for bile acids in the pathophysiology of cardiac dysfunction in cirrhosis,[13, 14] termed cirrhotic cardiomyopathy,[15, 16] which has a prevalence of ~50% according to some studies.[17, 18] Electrocardiographic abnormalities, more specifically prolonged QT interval is a key derangement of cirrhotic cardiomyopathy and is known to cause sudden death in adults [19, 20] and increases mortality risk in children[21] with liver failure.

An additional observation of this study is the fact that serum levels of UDCA are lower, while serum levels of non-UDCA bile acids are higher in patients with arrhythmias. This suggests that bile acid 'composition' is equally important as bile acid 'concentration' in the pathogenesis of rhythm disturbance. This subtle but important clinical finding adds to the growing body of literature supporting the therapeutic efficacy of UDCA. UDCA has traditionally been used as a hepatoprotective agent in human cholestatic liver diseases.[22] Recent rodent and human studies suggest that UDCA may have a cardioprotective role. It has been shown to protect rat neonatal cardiomyocytes from arrhythmogenic effects of TCA.[23] In a rat model of ischaemia-reperfusion injury, UDCA reduces cell death and apoptosis by Protein Kinase B (AKT)-mediated pathways.[24] A report published in 2012 in the *Journal of American College of Cardiology* shows that apart from being well tolerated, UDCA improves peripheral blood flow and is associated with improved liver function in patients with congestive heart failure (New York Heart Association (NYHA) Class II/III).[25] The Rainer study now adds a new facet to the biological importance, safety and therapeutic profile of UDCA.

The question that still remains unanswered is how these extracellular bile acids affect intracellular myocardial cell biology. It is possible that hydrophobic bile acids such as TCA, by virtue of their 'detergent'-like properties alter the composition and structure of the cardiomyocyte cell membrane causing a direct damage to the cardiac ion channels, thus affecting Ca^{2+} signalling as this[12] and other studies imply.[26–28] It is also possible that the bile acids exert intracellular effect on pathways that regulate Ca^{2+} homoeostasis and signalling through membrane receptors such as muscarinic receptors[29] or the newly discovered bile acid receptor TGR5 which is present in rodent, rabbit and human hearts.[1, 13, 30]

In summary, the observations made here help advance our understanding and knowledge of favourable as well as unfavourable effects of bile acids on the heart. These findings provide a springboard for conducting further in-depth studies looking into mechanisms of the bile acid-myocardial interaction, which will hopefully lead to rational therapeutic interventions which are seriously lacking in the field of cardiomyopathy and heart failure.

References

1. Watanabe M, Houten SM, Mataki C, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature. 2006; 439:484–9. [PubMed: 16400329]
2. Barnes S, Gallo GA, Trash DB, et al. Diagnositic value of serum bile acid estimations in liver disease. J Clin Pathol. 1975; 28:506–9. [PubMed: 1141454]

3. Neale G, Lewis B, Weaver V, et al. Serum bile acids in liver disease. Gut. 1971; 12:145–52. [PubMed: 5548561]
4. Legg, JW. On the bile, jaundice and biliary diseases. London: H.K. Lewis; 1879.
5. Wakim KG, Essex HE, Mann FC. The effects of whole bile and bile salts on the innervated and the denervated heart. Am Heart J. 1940; 20:486–91.
6. Joubert P. Cholic acid and the heart: in vitro studies of the effect on heart rate and myocardial contractility in the rat. Clin Exp Pharmacol Physiol. 1978; 5:9–16. [PubMed: 639363]
7. Joubert P. An in vivo investigation of the negative chronotropic effect of cholic acid in the rat. Clin Exp Pharmacol Physiol. 1978; 5:1–8. [PubMed: 639354]
8. Binah O, Rubinstein I, Bomzon A, et al. Effects of bile acids on ventricular muscle contraction and electrophysiological properties: studies in rat papillary muscle and isolated ventricular myocytes. Naunyn Schmiedebergs Arch Pharmacol. 1987; 335:160–5. [PubMed: 3561530]
9. Gorelik J, Harding SE, Shevchuk AI, et al. Taurocholate induces changes in rat cardiomyocyte contraction and calcium dynamics. Clin Sci (Lond). 2002; 103:191–200. [PubMed: 12149111]
10. Gorelik J, Shevchuk A, de SM, et al. Comparison of the arrhythmogenic effects of tauro- and glycoconjugates of cholic acid in an in vitro study of rat cardiomyocytes. BJOG. 2004; 111:867–70. [PubMed: 15270939]
11. Williamson C, Gorelik J, Eaton BM, et al. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. Clin Sci (Lond). 2001; 100:363–9. [PubMed: 11256973]
12. Rainer P, Primessnig U, Harenkamp S, et al. Bile acids induce arrhythmias in human atrial myocardium: implications for altered serum bile acid composition in patients with atrial fibrillation. Heart. 2013; 99:1685–92. [PubMed: 23894089]
13. Desai MS, Shabier Z, Taylor M, et al. Hypertrophic cardiomyopathy and dysregulation of cardiac energetics in a mouse model of biliary fibrosis. Hepatology. 2010; 51:2097–107. [PubMed: 20512997]
14. Zavecz JH, Battarbee HD. The role of lipophilic bile acids in the development of cirrhotic cardiomyopathy. Cardiovasc Toxicol. 2010; 10:117–29. [PubMed: 20414815]
15. Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. Semin Liver Dis. 2008; 28:59–69. [PubMed: 18293277]
16. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Postgrad Med J. 2009; 85:44–54. [PubMed: 19240290]
17. Desai MS, Zainuer S, Kennedy C, et al. Cardiac structural and functional alterations in infants and children with biliary atresia, listed for liver transplantation. Gastroenterology. 2011; 141:1264–72. [PubMed: 21762660]
18. Zardi EM, Abbate A, Zardi DM, et al. Cirrhotic cardiomyopathy. J Am Coll Cardiol. 2010; 56:539–49. [PubMed: 20688208]
19. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver International. 2003; 23:243–8. [PubMed: 12895263]
20. Zambruni A, Trevisani F, Caraceni P, et al. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol. 2006; 44:994–1002. [PubMed: 16510203]
21. Arikan C, Kilic M, Tumgor G, et al. Impact of liver transplantation on rate-corrected QT interval and myocardial function in children with chronic liver disease*. Pediatr Transplant. 2009; 13:300–6. [PubMed: 18537904]
22. Carey EJ, Lindor KD. Current pharmacotherapy for cholestatic liver disease. Expert Opin Pharmacother. 2012; 13:2473–84. [PubMed: 23094715]
23. Gorelik J, Shevchuk AI, Diakonov I, et al. Dexamethasone and ursodeoxycholic acid protect against the arrhythmogenic effect of taurocholate in an in vitro study of rat cardiomyocytes. BJOG. 2003; 110:467–74. [PubMed: 12742331]
24. Rajesh KG, Suzuki R, Maeda H, et al. Hydrophilic bile salt ursodeoxycholic acid protects myocardium against reperfusion injury in a PI3K/Akt dependent pathway. J Mol Cell Cardiol. 2005; 39:766–76. [PubMed: 16171810]

25. von HS, Schefold JC, Jankowska EA, et al. Ursodeoxycholic acid in patients with chronic heart failure: a double-blind, randomized, placebo-controlled, crossover trial. J Am Coll Cardiol. 2012; 59:585–92. [PubMed: 22300693]

26. Gazawi H, Ljubuncic P, Cogan U, et al. The effects of bile acids on beta-adrenoceptors, fluidity, and the extent of lipid peroxidation in rat cardiac membranes. Biochem Pharmacol. 2000; 59:1623–8. [PubMed: 10799661]

27. Ma Z, Lee SS, Meddings JB. Effects of altered cardiac membrane fluidity on beta-adrenergic receptor signalling in rats with cirrhotic cardiomyopathy. J Hepatol. 1997; 26:904–12. [PubMed: 9126806]

28. Ward CA, Liu H, Lee SS. Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy. Gastroenterology. 2001; 121:1209–18. [PubMed: 11677214]

29. Sheikh Abdul Kadir SH, Miragoli M, bu-Hayyeh S, et al. Bile acid-induced arrhythmia is mediated by muscarinic M2 receptors in neonatal rat cardiomyocytes. PLoS ONE. 2010; 5:e9689. [PubMed: 20300620]

30. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. J Biol Chem. 2003; 278:9435–40. [PubMed: 12524422]