Drug for heart is applicable to liver: Is it possible?

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With a better understanding of pathophysiology of disease, more and more off-labeled used drugs might have another potential role in the management for the other diseases, which have never been listed as indications for these drugs. One of the best examples is an "aspirin," which is a well-known antiinflammatory and antipyretic drug.[1] However, the aspirin causing antiplatelet side effect and subsequently resultant inhibition of thrombus formation in the cardiovascular (CV) system triggers this drug to be widely used as a primary prevention agent for patients with a high risk of episode of thromboembolic events.[2–4] Aspirin not only provides very apparent benefits on CV protection, aspirin is also suggested to offer the beneficial role in various troublesome diseases and clinical situations.[5] For example, many metabolism- and pregnancy-related diseases, such as polycystic ovary syndrome and preeclampsia have been successfully prevented by using aspirin.[6–8] Another example is prostaglandin E1 (misoprostol), which is often used in protection of stomach; however, it is often applied for induction of labor in off-labeled indication.[9] Therefore, Dr. Chang's study[10] attempting to use "ivabradine," an inhibitor to act on sinoatrial nodal cells and subsequently to slow down the heart rate, for the treatment of portal hypertension is interesting and worthy of discussion. In fact, this novel strategy related article[10] has been worthy of applause and is recognized as the best research work by the *Szu-Yuan Research Foundation of Internal Medicine* in 2020, and Dr. Chang also got this award at the Annual Conference of the *Chinese Medical Association* on June 9, 2020, held in Taipei, Taiwan.

Dr. Ching-Chih Chang and his colleagues using the artificial partial ligation of the portal vein to induce portal hypertensive rat model attempted to investigate the effect of ivabradine on the portal hypertension associated with hyperdynamic circulation and tachycardia.[10] After ivabradine treatment, heart rate and superior mesentery arterial flow were statistically significantly decreased compared to no treatment group; however, the other parameters, including mean arterial pressure, cardiac index, systemic vascular resistance, portal pressure, and serum levels of oxidative stress markers, including nitric oxide synthasis (NOS) or collateral vascular responsiveness to arginine vasopressin were not significantly altered between ivabradine treatment and no ivabradine treatment groups.[10] Although this research work showed the impressive finding, many uncertainties need further clarification.

At first, the proposal of Dr. Chang's study is reasonable, since portal hypertension is simply defined as an increase in the pressure gradient between port vein and inferior vena cava with subsequently increasing portal venous inflow, and finally leading to the development of a hyperdynamic circulation syndrome in the systemic circulation (the arterial vasodilation and reduced central blood volume mimicking a physiological effective hypovolemia),[11] suggesting that pure portal hypertension is also a disease of cardiovascular system. Although it is novel, it is logic.

Second, before attempting to use unindicated molecules in the management of other disease, preclinical studies might be an easy way to test our hypothesis and subsequently investigate their effects. In fact, for portal hypertension, there are many preclinical studies, including Dr. Chang's group, available in the literature.[10,12,13] They continued to focus on therapeutic effects of these unindicated molecules on portal hypertension. However, we should be well informed that only a few molecules made it into human clinical trials. Moreover, many of them are limited to target splanchnic hyperemia.[14] Schwabl and Laleman have extensively reviewed theses potential novel therapies for portal hypertension, including nonselective ß blockers, vasopressin analogues, and somatostatin analogues.[14] The authors recognized that these candidate molecules can not be limited to one particular setting, because of complex and complicated disease patterns of portal hypertension.[14] Additionally, these potential candidates can be used for a long time without losing its effectiveness, with a low risk for drug-drug interaction, and as well as with the most important issue of safety to be taken.[14]

Dr. Chang' study focused on one potential molecule-ivabradine, a first-in-class blocker of the hyperpolarization-activated cyclic nucleotide-gated channel, modulating the heart rate in the sinoatrial node, on the therapeutic effect of rats with portal hypertension.[10] It is not surprising to note that the results of their study were only limited to improve some parameters of portal hypertension, hinting the lower chance of success in clinics. In fact, it is well known that the currently available drug targeting the dynamic component of portal hypertension is far from satisfactory results; thus the consideration of the using add-on therapy combinations may be a better choice. Premkumar's recent publication may be one of examples.[15] The authors tested the therapeutic effect by using the combination therapy with ß blocker and ivabradine, and the results showed this combination can successfully improve cardiac function, decrease the risk of encephalopathy, and acute kidney injury, and of most importance, this strategy targeted heart rate reduction with combination results in better overall survival.[15]

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Finally, I congratulated the success of Dr. Chang's work. This continuous evolving research, let us speculate that the successful treatment of portal hypertension undoubtedly will be reached.

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