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# The future treatment of portal hypertension

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Increased understanding of the hyperdynamic circulation syndrome has resulted in novel therapeutic approaches, some of which have already reached clinical practice. Central to the hyperdynamic circulation syndrome is an imbalance between the increase in different vasodilators (foremost among which is nitric oxide) and the compensatory increase in vasoconstrictors—usually accompanied by a blunted response. This chapter discusses the role of endothelin in the pathogenesis of the syndrome and in future treatment approaches. A relatively new area of research in this field is the role of infection and inflammation in the initiation and maintenance of the hyperdynamic circulation syndrome. The use of antibiotics in the setting of acute variceal bleeding is standard practice. Studies have suggested that chronic manipulation of the intestinal flora could have beneficial effects in the treatment of portal hypertension. The bile salts are another novel and interesting target. Although their vasoactive properties have been known for some time, recent data demonstrate that their effects could be central in the pathogenesis of the hyperdynamic circulation syndrome, and that manipulation of the composition of the bile acid pool could be a therapeutic approach to portal hypertension. Finally, hypoxia and angiogenesis play a role in the development of portal hypertension and the formation of collaterals. This role needs to be further defined but it appears likely that this phenomenon is yet another target for therapeutic intervention.

**Key words:** antibiotics; bile salts; endothelin; hyperdynamic circulation; infection; inflammation; innate immunity; nitric oxide; pharmacotherapy; portal hypertension.

## INTRODUCTION

Almost 20 years ago we reviewed the pharmacology of treatment of portal hypertension.[1] We identified potential candidates to replace non-selective β-blockers[2] and many drug candidates that had an effect on portal pressure. We predicted that

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combination therapy would be the way of the future. This prophecy certainly did not fully pan out. The only combination treatment validated in randomized clinical trials was that of a non-selective β-blocker with nitrates—a combination that had equal or superior effects to standard treatment in some trials.[3–5] Spironolactone—the preferred diuretic in the treatment of ascites—also lowers portal pressure[6] but its effects on clinical events in portal hypertension have yet to be investigated in a large-scale clinical trial.

Given the many potential targets, we still believe that combinations of different drugs will increase efficacy and—if well selected—decrease side effects. In this chapter, we propose some novel approaches based on animal experiments, some of which have a proof of principle available in humans. In clinical practice, however, non-selective β-blockers remain the mainstay of treatment of portal hypertension. An approach tailored to the patient based on repeated measurement of portal pressure can increase the efficacy of this treatment.[7] Haemodynamic measurement of the efficacy of treatment has been suggested to be of prime importance and to predict survival[8,9] but further clinical studies are needed. This review is not all inclusive: we have focused on the main vasoconstrictor and vasodilator, namely endothelin and nitric oxide; other potential candidates are shown in Table 1.

## IS PORTAL HYPERTENSION AN INFECTIOUS PROCESS?

In 1991, Vallance and Moncada proposed that the hyperdynamic circulation of portal hypertension could be due to induction of nitric oxide synthase by bacteria or bacterial products such as endotoxin.[14] Indeed, bacterial translocation is frequent in patients with

**Table 1.** Vasoconstrictors and vasodilators implicated in the hyperdynamic circulation syndrome.

| | Reference |
|---|---|
| *Vasoconstrictor* | |
| Endothelin | 10–13 |
| Norepinephrine (noradrenaline) | 15 |
| Angiotensin | 17 |
| Vasopressin | 19 |
| Serotonin | 22, 23 |
| Somatostatin | 24 |
| Urotensin | 27 |
| *Vasodilator* | |
| Nitric oxide | 14 |
| Carbon monoxide | 16 |
| Hydrogen disulfide | 18 |
| Adrenomedullin | 20, 21 |
| Bile salts | See text |
| Calcitonin gene-related peptide | 25, 26 |
| Glucagon | 28 |
| Eicosanoids | See text |
| γ-Aminobutyric acid | 29 |
| Cannabinoids | 30–32 |

All are potential targets for future therapeutic interventions but only endothelin and nitric oxide are covered in depth in this review.