Portal hypertension is characterized by increased portal pressure due in part to a reduction in mesenteric vascular resistance. It is generally accepted that in humans and in animal models of portal hypertension, the reduced vascular resistance is due to a marked pressor hyporesponsiveness in vivo. However, whether this vascular hyporesponsiveness is directly related to a reduction in the contractile potency of individual splanchic or systemic vessels to various circulating vasoconstrictors remains controversial. Previous studies using prehepatic portal hypertensive animals and cirrhotic animals have generally reported a similar diminished vascular response to vasoconstrictors in isolated vessels from these animals in vitro. The study in this issue of Clinical Science by Connolly et al. [1] is particularly significant since it is one of only a few studies to definitively demonstrate that the pressor responsiveness of isolated endothelial intact aortic rings is either unchanged or significantly enhanced in two portal hypertensive rat strains in vitro. The paper describes how isolated aortic rings from an experimental rat model of portal hypertension do not exhibit a difference in the contractile potency of KCl, phenylephrine and noradrenaline. However, they do exhibit a significant increase in the maximal contractile response to these vasoconstrictors. Moreover, the differences in vascular reactivity were independent of agonist or strain of animal. The authors conclude that their results question the widely held belief that the diminished responsiveness to vasoconstrictors reported in portal hypertensive rats in vivo is due to a diminished responsiveness at the level of the vascular smooth muscle.

A marked pressor hyperresponsiveness in vitro has also been reported in portal hypertensive rats for several vasoconstrictors including 5-hydroxytryptamine, U46199 and endothelin [2–4]. Moreover, in cirrhotic rats with portal hypertension, the sensitivity of the contractile force to noradrenaline was significantly enhanced concomitant with increased Ca²⁺ sensitivity [5]. The reason for the discrepancies between these and previous in vitro studies are at present unknown. Connolly et al. [1] suggest two main possibilities. First, the data may represent different ends of the spectrum in that there may be in reality no overall change in the vascular responsiveness in vitro. Indeed, several studies have reported no change in the overall pressor reactivity of these vessels [6]. In addition, unlike the current study, several previous studies do not pretreat the aortic rings with indomethacin, propranolol and cocaine during equilibration, suggesting that differences in methodologies may account in part for these discrepancies. Alternatively, there may be subtle changes occurring after ligation of the portal vein in these animals which are dependent on the degree and duration of the stenosis. What is clear, however, is that the results of the current study suggest that the marked pressor hyporesponsiveness observed in vivo is most probably not due to a diminished ability of these vessels to contract in vitro.

How does one explain the apparent discrepancy between the in vivo and the in vitro data? One explanation is the increase in the vasodilator potency of several key vasodilators, including nitric oxide and prostacyclin, both of which are up-regulated in portal hypertensive vessels [7–9]. More importantly, inhibition of either of these pathways results in a significant attenuation of the pressor hyporesponsiveness in vivo [9]. Furthermore, physiological antagonism of endogenous vasoconstrictors by nitric oxide or prostacyclin would be diminished in vitro, in particular, if either haemodynamic forces (such as shear stress due to the increased blood flow) or portal-systemic shunts were originally responsible for increasing the level of these vasodilator substances in vivo. Another explanation may involve arterial structural responses due to altered blood flow that are accompanied by modified reactivity of arterial smooth muscle which entails a hyperresponsiveness to maximal stimulation with neurogenic stimuli [10]. Although no change in smooth muscle cell mass was reported in the current study, it is conceivable that subtle arterial remodelling due to chronic elevations in blood flow, typical of portal hypertension, could account for the exaggerated reactivity of these vessels in vitro. Increased circulating levels of endogenous vasoconstrictors may also be in part responsible for the marked pressor hyporesponsiveness observed in vivo. Elevated levels of endogenous vasoconstrictors in portal hypertensive animals will almost certainly impact on the pressor responsiveness of exogenous administration of the same vasoconstrictor in vivo. Consistent with this observation, enhanced levels of vasoconstrictor substances are apparent in portal hypertensive animals [11] and humans [12].

Since the majority of isolated ring studies have been performed on endothelial intact vessels, there are several possible endothelial-dependent mechanisms by which the contractile response to vasoconstrictors may be exaggerated in vitro. Most notably, endothelial receptor transmembrane signalling resulting in vascular relaxation may be decreased in portal hypertensive vessels. How-
However, this seems unlikely since endothelial receptor- and G_α-protein-induced nitric oxide-dependent relaxation is enhanced in portal hypertensive vessels [13]. Alternatively, pressor hormone receptor G-protein coupling may be increased in portal hypertensive vessels. Indeed, a dramatic increase in G_α, G_βγ, and G_α protein expression and phospholipase C activity has been reported in portal hypertensive vessels consistent with an enhanced pressor response *in vitro* [14,15]. Paradoxically, Huang et al. [16] suggest that attenuation of the contractile response to vasoconstrictors in portal hypertensive rats is reflected in the suppression of phosphoinositol metabolism. Finally, endothelial-derived vasodilators may also cause adaptive changes in the responsiveness of portal hypertensive vessels to vasoconstrictors. For example, chronic exposure of an isolated aorta or superior mesenteric artery to nitric oxide results in an exaggerated vascular response to endothelin *in vitro* [17].

In summary, the study by Connolly et al. [1] represents a significant contribution to the field of portal hypertension in that it questions whether the marked pressor hyporesponsiveness observed *in vivo* is due to a diminished contractile response of the hyperemic vessel. While the current study rules out a change in vasoconstrictor receptor expression, additional work will be required to delineate the exact mechanism(s) for the pressor hyporesponsiveness to some vasoconstrictors *in vitro* and the potential role of the vascular endothelium in mediating this response.

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REFERENCES