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## Vasopressin analogues in the treatment of hepatorenal syndrome and gastrointestinal haemorrhage

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Bleeding of oesophageal varices and hepatorenal syndrome are most dramatic complications in gastroenterology. They develop in consequence of progressively increasing blood flow entering the vasodilated splanchnic bed and the portal vein where blood flow meets intrahepatic resistance. Porto-systemic collateral veins are formed to bypass the cirrhotic liver. Intravascular pressure is very high in these collaterals, causing the venous walls to expand into esophageal varices, which eventually may rupture and bleed. This splanchnic blood pooling generates hypovolemia in the central and arterial system, initiating activation of the renin-angiotensin-aldosterone and sympathetic nervous system. These compensatory mechanisms induce renal vasoconstriction, followed by hypoperfusion of the kidneys and development of hepatorenal syndrome. Vasoconstrictors like terlipressin inhibit splanchnic blood flow, thus reducing portal and variceal pressure, which is followed by termination of variceal bleeding, by normalization of central and arterial blood volume and by an improvement of kidney function and hepatorenal syndrome.

**Key words:** gastrointestinal hemorrhage; hepatorenal syndrome; oesophageal variceal bleeding; portal hypertension; terlipressin; vasoactive compounds; vasopressin.

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### ALTERED HAEMODYNAMICS IN PATIENTS WITH LIVER CIRRHOSIS

Portal hypertension is the most frequent symptom of liver cirrhosis. Patients with advanced liver cirrhosis develop portal hypertension with a pressure of more than

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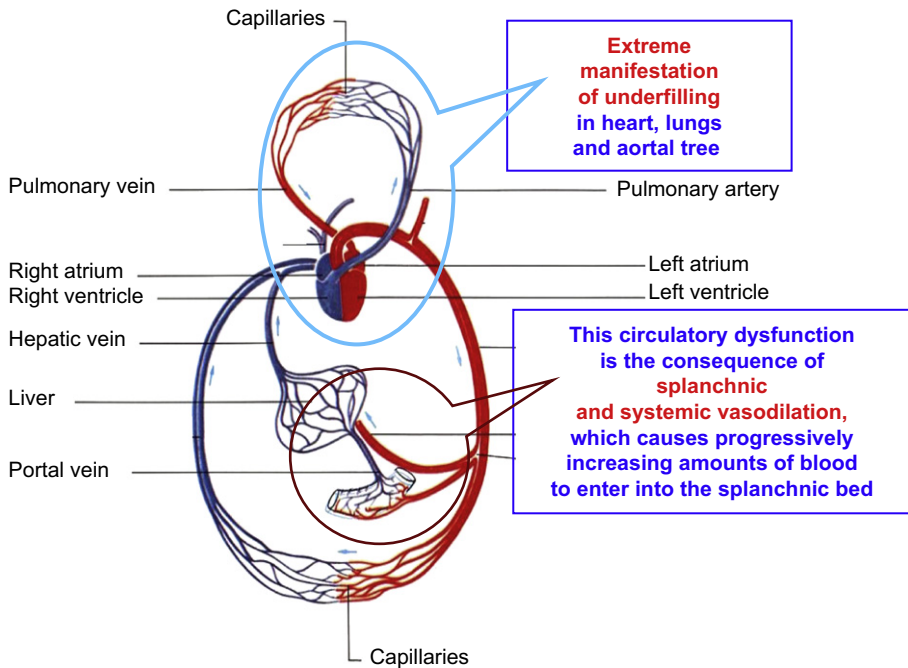
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8 mm Hg. On account of the elevated intra-hepatic resistance the blood circulation develops porto-systemic collaterals between the portal vessel and the systemic venous return. Intravascular pressure is very high in these collaterals, causing the venous walls to expand into oesophageal varices. Variceal walls are thin, vulnerable and tend to rupture easily, inducing bleeding and accounting for a high mortality rate.<sup>1</sup>

Blood flow within the cardiovascular system is disturbed in patients with liver cirrhosis and portal hypertension. Splanchnic arteries and arterioles are dilated, vascular resistance is decreased and blood volume in the splanchnic blood vessels is elevated. Elevated blood flow meets intrahepatic resistance, which causes portal pressure to increase. Splanchnic arterial vasodilation not only increases portal hypertension, but impairs the systemic arterial blood circulation as well. The result is the development of a so called “hyperdynamic blood circulation” with elevated cardiac index, decreased vascular resistance and arterial hypotension (Figure 1). The central and arterial blood volume, which is equivalent to the effective blood volume and comprises the blood in heart, lungs and aortal tree, is reduced.<sup>2-8</sup>

Portal hypertension is associated with the following cardiovascular impairments:

- blood vessels in the splanchnic area are dilated<sup>2,5,7,8</sup>,
- peripheral blood volume is elevated<sup>2,5,7,8</sup>,
- central and arterial blood volume is reduced<sup>2,4-8</sup>,
- systemic vascular resistance is decreased<sup>2,4,6-8</sup>,



**Figure 1.** Disturbed blood flow within the cardiovascular system in patients with liver cirrhosis and portal hypertension. Redrawn from<sup>14</sup> with permission.

- systolic, diastolic and mean arterial blood pressure are reduced, particularly throughout the day, less during the night<sup>4</sup>,
- heart rate and cardiac index are elevated<sup>6,9,10</sup>,
- arterial compliance is elevated<sup>3,11</sup>,
- blood flow to the kidneys and to other life-essential organs is reduced<sup>12,13</sup>.

## SPLANCHNIC HYPERVOLEMIA – CENTRAL HYPOVOLEMIA

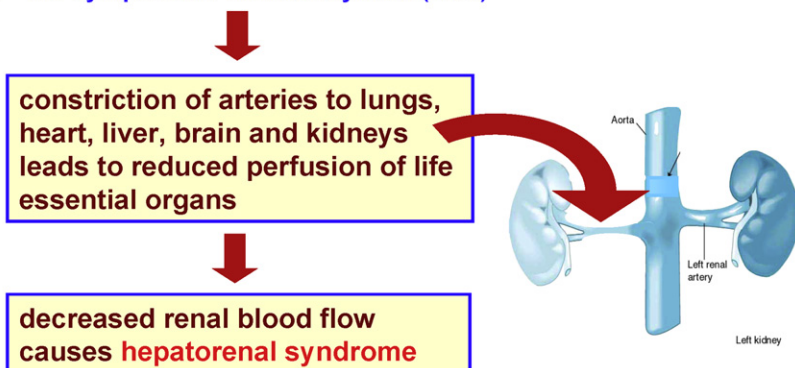
Circulatory dysfunction in patients with portal hypertension is the consequence of peripheral and splanchnic arterial vasodilation. The cause for this vasodilation is thought to be due to systemic and locally acting vasodilators like nitric oxide, glucagon, calcitonin-gene-related peptide, substance P, vasoactive intestinal peptide, tumor necrosis factor, adrenomedullin and the non-adrenergic, non-cholinergic neurotransmitter system.<sup>15</sup>

Splanchnic vasodilation leads to reduced vascular resistance and to increased blood volume in mesenteric, skin and muscular blood vessels. This blood pooling in the periphery generates hypovolemia in the central and arterial system with decreased systolic and diastolic blood pressure<sup>4</sup>, initiating compensatory activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). This compensatory mechanism induces renal vasoconstriction which is followed by hypoperfusion of the kidneys and other vital organs.<sup>2,4,6,16,17</sup> Compensatory activation of vasoconstrictive hormonal systems may also impair intra-hepatic haemodynamics<sup>15</sup> through increase in intrahepatic vascular resistance, thus intensifying portal hypertension. In consequence a vicious circle develops with continued worsening of the haemodynamic situation and ultimately with development of ascites and hepatorenal syndrome (Figures 2 and 3).

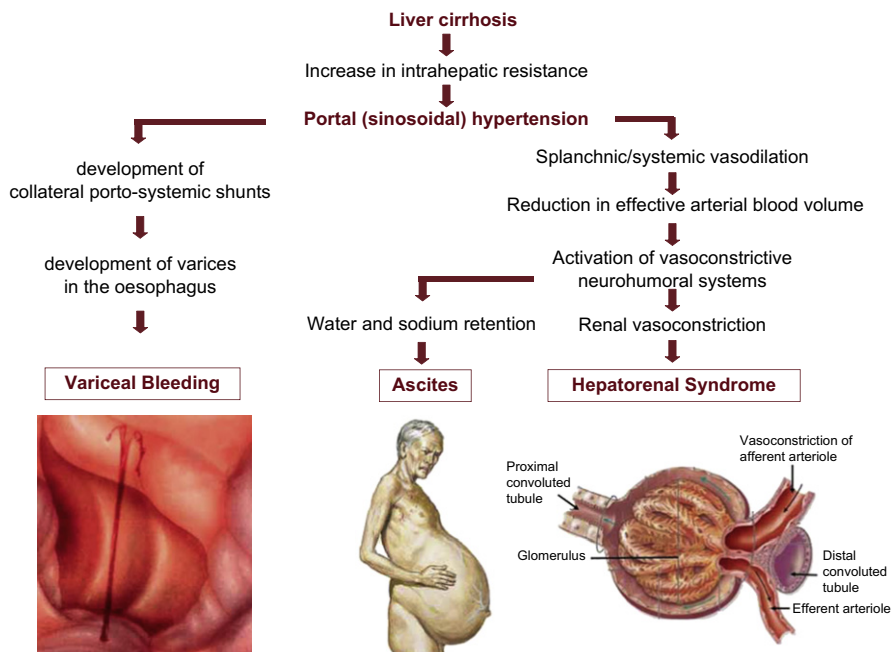
### Underfilling of central and arterial blood vessels in portal hypertension...

... leads to compensatory activation of

1. the renin-angiotensin-aldosterone-system (RAAS)
2. the sympathetic nervous system (SNS)



**Figure 2.** Development of hepatorenal syndrome as a consequence of central and arterial hypovolaemia.



**Figure 3.** Development of oesophageal varices, ascites and hepatorenal syndrome. Graphics with permission for variceal bleeding from<sup>18</sup> and for ascites from <http://www.netterimages.com/image/1157.htm> and for figure of renal corpuscle from McGraw-Hill Publishers, In: Mckinley, Michael: Human Anatomy 2/E, 2008.

## THERAPY OF ACUTE VARICEAL BLEEDING AND HEPATORENAL SYNDROME WITH VASOACTIVE COMPOUNDS

### Mechanism of action

The reason for portal hypertension is elevated blood flow into the splanchnic area which meets intrahepatic resistance and thus causes portal pressure to increase. An ideal medication should

- constrict splanchnic blood vessels to reduce inflow of blood into the splanchnic area and
- dilate intrahepatic vessels, thus, stimulating blood flow through the liver.

Splanchnic vasoconstriction reduces blood flow into the portal vein, thus reducing portal pressure, thereby reducing vascular pressure in the porto-systemic collateral veins and in the oesophageal varices leading to arrest of bleeding. Inhibition of blood flow into the splanchnic area prevents depletion of central and arterial blood volume, thus correcting hypovolaemia and reducing RAAS and SNS activity, which subsequently leads to lower intrahepatic and intrarenal resistance. The result is an improvement of organ perfusion – including perfusion of kidneys and liver – an improvement of the hyperdynamic cardiovascular situation and an improvement of survival rate (for review see<sup>19</sup>).

## Treatment of bleeding oesophageal varices with vasoactive compounds

Variceal bleeding is one of the most dramatic complications in gastroenterology and has a high mortality rate.<sup>1</sup> Early treatment with vasoactive drugs can save life, when skilled endoscopists are not immediately available. Vasoactive drugs, like vasopressin, the vasopressin analogue terlipressin, somatostatin or the somatostatin analogue octreotide, are not only indicated as first choice emergency treatment<sup>1</sup>, but they also increase the success rate of endoscopic treatments.<sup>20</sup> Whereas efficacy and mechanisms of action of vasopressin and terlipressin to arrest haemorrhage and to improve the disturbed cardiovascular situation of cirrhotic patients, including hepatorenal syndrome, are well documented, efficacy and mechanisms of action of somatostatin and octreotide remain unclear and uncertain (for reviews see<sup>1,19</sup>).

### *Vasopressin and terlipressin*

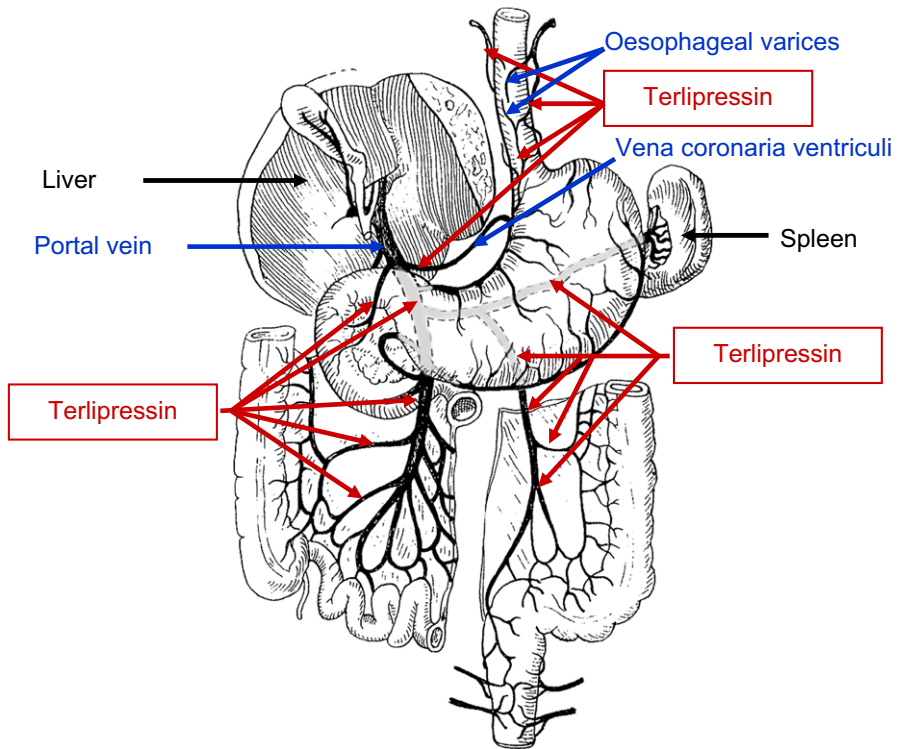
Vasopressin and terlipressin are the only vasoactive compounds, which have been approved by regulatory agencies for the treatment of bleeding oesophageal varices. However, in clinical studies vasopressin treatment is shown to be associated with adverse effects, like release of coagulating factors<sup>21</sup>, arterial hypertension, angina pectoris, arrhythmia as well as cardiac and peripheral ischemia.<sup>22</sup> In contrast, terlipressin application seems to be more effective than vasopressin<sup>22,23</sup>, without showing the previously mentioned adverse events<sup>22</sup> and was shown to have a longer half life<sup>24</sup> making it to the preferred clinically used vasoconstrictor.

Blei et al<sup>25</sup> compared the effects of vasopressin and terlipressin on splanchnic hemodynamics in dogs and demonstrated that terlipressin reduces portal venous pressure and blood flow in the splanchnic area without inducing contra-regulatory feedback effects. Whereas vasopressin reduced oxygen pressure in the liver of dogs, oxygen pressure was not affected by treatment with terlipressin.<sup>26</sup> In contrast to vasopressin terlipressin was shown to compensate the reduced portal blood flow to the liver by increasing blood flow in the hepatic artery.<sup>25-28</sup>

Terlipressin is a synthetic 12 amino acid peptide (1-triglycyl-8-lysine-vasopressin) derived from the natural hormone lysine-vasopressin. Terlipressin is predominantly a pro-drug, which seems to have only low pharmacological activity on its own.<sup>29</sup> Because the active metabolite lysine-vasopressin is gradually released over several hours<sup>24</sup>, typical vasopressinergic adverse events such as release of coagulation factors and cardiotoxic ischemia are avoided.<sup>21,22</sup> Due to its vasoconstrictive activity via V<sub>1</sub>-receptors on vascular and extra-vascular smooth muscle cells terlipressin was shown to reduce blood flow into the portal vein<sup>25,27</sup> and, thus, to reduce portal venous pressure and blood flow through porto-systemic shunts<sup>25,27</sup> (Figure 4).

Terlipressin was shown not only to constrict splanchnic vessels, but also to dilate intrahepatic vessels, and, thus, to reduce intrahepatic resistance and to facilitate blood flow through the liver.<sup>30</sup> Liver blood volume was reported to be increased by up to 12% within seconds after terlipressin application.<sup>30</sup>

Terlipressin seems to stimulate intrahepatic microcirculation by relaxing the stellate cells.<sup>30</sup> This may lead to dilation of the sinusoids and to an increase in blood volume concomitant with a reduction of haemodynamic resistance in the liver sinusoids. Consequence is an elevated inflow of blood into liver (12%) and thorax (6%).<sup>30</sup> An increase in thoracic blood volume may affect volume- and baroreceptors and thereby attenuate the activated RAAS and SNS vasoconstrictor systems. The result is a reversal of central and arterial hypovolaemia and interruption of the hyperdynamic vicious circle.



**Figure 4.** Terlipressin constricts the splanchnic blood vessels thereby reducing blood flow to the portal vein and decreasing pressure in the portal vein, the collateral vessels and the varices. Redrawn from<sup>19</sup>, with permission.

Terlipressin is approved and marketed in many countries for the treatment of oesophageal variceal hemorrhage (OVH) since the early 1980s. Acute OVH is a serious complication of portal hypertension in patients with liver cirrhosis with a 20% to 30% mortality rate.<sup>1</sup> Terlipressin is recognized by clinical experts worldwide as one of the standard therapies available for this condition, and represents the only compound to have shown a survival benefit compared to placebo.<sup>22,31–34</sup> Terlipressin has been shown to arrest variceal bleeding in the acute emergency state<sup>1,22,23,31–34</sup> and to support endoscopic treatment.<sup>20</sup> The effect of terlipressin starts within a few minutes<sup>30,35</sup> and lasts over 4 to 6 hours.<sup>36</sup>

In contrast to other pharmacological treatments, which must be applied in form of continuous i.v. infusion, terlipressin can be applied i.v. as a bolus.

#### *Somatostatin and octreotide*

Although somatostatin and octreotide, two growth hormone release inhibitors, are not approved for treatment of variceal bleeding, they are occasionally used for this indication, particularly in countries where terlipressin is not available. Somatostatin and octreotide were shown to lower portal and mesenteric blood flow and to elevate splanchnic vascular resistance in animals and in healthy subjects.<sup>37,38</sup> However, in patients with portal hypertension and variceal bleeding hemodynamic effects of

somatostatin and octreotide remain unclear. Most hemodynamic studies with somatostatin<sup>39–43</sup> or octreotide<sup>35,44</sup> were unable to show pressure reduction in portal vein, liver veins or in oesophageal varices. Kleber et al<sup>45</sup> even reported an increase in variceal pressure during infusion of somatostatin and Primignani et al<sup>46</sup> reported an increase in variceal pressure during infusion of octreotide.

The only proven hemodynamic effects of octreotide in cirrhotic patients with portal hypertension seem to be prevention of postprandial splanchnic hyperaemia and prevention of the meal-induced increase in portal venous pressure<sup>47,48</sup>, which both are probably due to the inhibitory effect of octreotide on postprandial glucagon release.<sup>38</sup>

Octreotide was shown to rapidly desensitize somatostatin receptors, which may also explain its uncertain haemodynamic effects.<sup>49</sup> Baik et al<sup>50</sup> reported that treatment of cirrhotic patients with a bolus of 100 µg octreotide, followed by continuous infusion of 250 µg/hour, reduced the hepatic venous pressure gradient (HVPG) and portal blood flow (PBF) for less than 5 minutes, after which both parameters had returned to baseline. Bolus injection of 2 mg terlipressin, on the other hand, reduced HVPG and PBF within one minute and both parameters remained low throughout the total observation period of 25 minutes.<sup>50</sup>

Haemodynamic effects of somatostatin on portal vessels, on collateral porto-systemic shunts and on oesophageal varices were shown to last only from seconds to a few minutes: Bolus injection of 250 µg somatostatin reduced intravariceal pressure only for 3 minutes<sup>51</sup> and showed some effect on portal pressure and collateral blood flow<sup>52</sup>, however, only for 1–3 minutes.<sup>53,54</sup> A study performed by Villanueva et al<sup>55</sup> in patients with acute variceal bleeding showed that the normally used treatment dose of 250 µg/h somatostatin had no effect on portal pressure reduction. Reduction of portal pressure was partly seen at the high dose of 500 µg/h<sup>55</sup>, however, at a lower magnitude compared to that which is seen in patients treated with 2 mg terlipressin.<sup>55</sup>

Results from placebo-controlled studies with somatostatin as therapy for acute variceal bleeding are controversial and only one placebo-controlled study with octreotide exists. Infusion of 250 µg somatostatin per hour for 24 to 30 hours plus additional 250 µg bolus injection showed no advantage over placebo treatment.<sup>56,57</sup> Only treatment for longer periods (5 days) and with higher doses of somatostatin (500 µg per hour) reduced variceal bleeding better than placebo.<sup>58–60</sup> Only one double-blind randomized controlled trial with octreotide has been published to date, showing not more effects than placebo in controlling and preventing early recurrent variceal bleeding.<sup>61</sup> Meta-analysis of all available data published on placebo-controlled studies confirmed the doubt on somatostatin and octreotide as appropriate therapy to stop acutely bleeding oesophageal varices.<sup>62</sup>

#### *Treatment of bleeding oesophageal varices with vasoactive compounds: conclusion*

#### **Practice points**

- Bleeding of oesophageal varices is one of the most dramatic complications in gastroenterology and has a high mortality rate.<sup>1</sup>

- The only approved drugs to arrest variceal bleeding are vasopressin and terlipressin. Treatment with terlipressin seems to be preferable most likely due to better efficacy<sup>22,23</sup>, longer effects<sup>24</sup> and less adverse effects compared to vasopressin<sup>21,22</sup>.
- Terlipressin is not only indicated as first choice emergency treatment<sup>1</sup>, but it has also been shown to increase the success rate of endoscopic treatments<sup>20</sup>.
- Studies demonstrate that terlipressin treatment decreases the mortality rate<sup>22,31–33</sup> and may help especially when skilled endoscopists are not immediately available.
- In particular in an emergency clinical situation, terlipressin, given as an i.v. bolus and leading to a fast onset of effect, makes this medication very convenient for clinicians.<sup>31</sup>
- Although somatostatin and octreotide are not approved for treatment of variceal bleeding, they are occasionally used for this indication, particularly in countries where terlipressin is not available. However, efficacy and mechanisms of action to arrest haemorrhage and to improve the disturbed cardiovascular situation of cirrhotic patients remain unclear and uncertain for somatostatin and octreotide<sup>1,35,37–62</sup> whereas those for terlipressin are well documented and understood<sup>1,6,9,10,14,19–36</sup>.
- Terlipressin has been shown to stimulate kidney function and to prolong survival time in patients with bleeding oesophageal varices<sup>1,22,31–33</sup> while no such promising effects were observed with somatostatin or octreotide.<sup>1,56,57,59,62</sup>
- Based upon these clinical findings terlipressin is the preferred compound which has been shown in many studies to stop bleeding<sup>1,20,22,23,31–34,36</sup> and to reduce mortality in patients with bleeding oesophageal varices.<sup>1,22,31–33</sup>

### Research agenda

- Based on the observation that terlipressin not only stops variceal bleeding, but also reduces portal and variceal pressure further research is warranted to evaluate the effect of short term treatment with terlipressin for 3 days versus long term treatment for 5 to 10 days on occurrence of rebleeding.
- Further research is warranted on the effect of early treatment with terlipressin, i.e. when patients are picked up by the mobile emergency unit, versus late treatment, i.e. after time consuming endoscopic diagnosis, on time to arrest bleeding, prevention of rebleeding and mortality.

### Treatment of hepatorenal syndrome (HRS) with vasoactive compounds

HRS is the development of renal dysfunction in patients with end-stage liver cirrhosis in the absence of any other cause of renal pathology and has a poor prognosis.<sup>65,66</sup> In these patients impairment of kidney function is of reversible functional rather than

irreversible structural nature since it is triggered by a disturbance in the distribution of blood volume rather than by intrinsic renal pathology.

Two types of HRS have been described. Type 1 is characterized by rapid deterioration of renal function with marked increase in serum creatinine, azotemia, low urine output, dilutional hyponatremia and marked sodium retention, and by a short survival time once developed.<sup>66</sup> HRS type 1 is diagnosed by criteria established by the International Ascites Club in 1996.<sup>67</sup> Type 2 is a more stable clinical form with less severe renal failure and a longer survival time, typically occurring in patients with relatively preserved liver function.<sup>67</sup> The likely pathogenic mechanism leading to HRS is renal vasoconstriction secondary to marked arterial vasodilation and hypervolemia in the splanchnic vascular bed. Splanchnic hypervolemia generates central hypovolemia with decreased systolic and diastolic blood pressure and activation of RAAS and SNS. The thereby induced renal vasoconstriction is followed by hypoperfusion, worsening of renal haemodynamics and occurrence of renal failure (Figures 2 and 3). Activation of RAAS and SNS also leads to sodium and water retention and to impaired glomerular filtration rate, further aggravating the already compromised renal function. The median survival time after development of HRS type 1 is less than 2 weeks and most patients die while awaiting liver transplantation.<sup>66</sup>

#### *Vasopressin and terlipressin*

Therapy of choice for HRS patients is liver transplantation.<sup>67–69</sup> However, HRS type 1 patients may not survive long enough to receive a liver transplant, thus, reversing HRS and bridging the time to liver transplantation with a pharmacological therapy would be an important tool in the armamentarium of hepatologists. Also for patients who are not suitable for a transplant such a medication would represent an important, if not the only, therapy available to extend life-expectancy.

Preliminary studies have shown that the administration of splanchnic vasoconstrictors such as the vasopressin analogues ornipressin and terlipressin, in combination with volume expanders, improves renal function in patients with HRS and may be used to bridge the time until liver transplantation can be performed.<sup>63,64,69–80</sup>

Splanchnic vasoconstriction reduces blood flow from the central area into the splanchnic area. In consequence, central and arterial hypovolaemia is corrected and activation of the RAAS and the SNS are reduced, leading to lower intrahepatic and intrarenal resistance. The result is an improvement of organ perfusion, including perfusion of the kidneys and the liver, an improvement of the hyperdynamic cardiovascular situation and reversal of HRS.

Already in 1968<sup>81</sup> and 1972<sup>82</sup>, it was shown that the vasopressin analogue octapressin (2-L-phenylalanine-8-L-lysine-vasopressin) stimulated renal blood flow and improved renal function in cirrhotic patients. Two decades later, Lenz et al<sup>71,72</sup> observed similar beneficial effects of ornipressin, another synthetic analogue of vasopressin with ornithine in position 8 of the cyclic nonapeptide, on renal function in cirrhotic patients with decompensated liver cirrhosis. In 1999 Gülberg et al<sup>73</sup> recommended ornipressin plus dopamine as a useful therapeutic option in patients with HRS type 1, especially as bridge to liver transplantation.

In recent years, terlipressin has been shown in several clinical studies<sup>63,64,69,70,74–80,83</sup> – including prospective, randomized, placebo-controlled studies<sup>84–87</sup> – to be effective in reversing HRS, preferentially in combination with albumin.<sup>63</sup> Most likely due to its lower ischemic side effect profile<sup>78,79</sup>, but similar vasoconstrictive potency

as ornipressin<sup>78,79</sup>, terlipressin is now the preferred compound and represents the medication most widely studied in clinical trials including more than 350 patients with HRS.<sup>63,64,69,70,74–80,83–87</sup> Very recently terlipressin was also shown to improve renal function in patients with ascites without HRS.<sup>88</sup>

In summary, three types of treatment responses can be observed when terlipressin and albumin are given to patients with HRS:

1. Complete reversal of HRS occurs in approximately 50–80% of patients leading to an improved survival.<sup>69,70,80,83,84,87</sup>
2. Once treatment is discontinued, renal failure may recur, however, re-treatment with terlipressin leads again to improvement of renal function.
3. Partial response is often followed by relapse of renal failure.

Terlipressin moves excess blood from the splanchnic vascular compartment to the central and arterial vascular compartment, where blood is needed, by constricting blood vessels in the splanchnic area. As a consequence, treatment with terlipressin refills the central arteries, reduces the vasoconstrictive activity of the RAAS and the SNS and thus, restores blood supply to life essential organs, including liver and kidneys.

Administration of terlipressin in patients with HRS has been shown

- to increase creatinine clearance and to reduce serum levels of creatinine below 1.5 mg/dl<sup>63,64,69,70,74–79,83–87</sup>,
- to improve the overall cardiovascular function *via* an increase in mean arterial blood pressure and *via* inhibition of plasma renin activity and lowering of plasma levels of aldosterone and noradrenalin<sup>63,76,78,84,87</sup>
- to stimulate glomerular filtration rate<sup>76,78,79,83</sup>
- to stimulate natriuresis<sup>75,79</sup> and urine excretion<sup>63,64,75,76,79,84</sup>, parameters known to improve hepatorenal syndrome<sup>69,75,77–79</sup> and
- to improve survival.<sup>69,70,80,83,84,87</sup>

Of particular interest is the observation that in many of these patients, treated with terlipressin and volume expanders, the improved cardiovascular situation persisted and hepatorenal syndrome did not recur following discontinuation of the treatment.<sup>15,69,83,85</sup> It has also been shown that the lower pre-treatment serum levels of creatinine were, the higher was the probability of terlipressin-treatment success.<sup>86</sup> For each 1 mg/dl increase in pre-treatment serum creatinine levels the probability for HRS reversal decreased by 39%<sup>86</sup> and the probability for overall survival decreased by 40% [Poster to<sup>86</sup>]. Patients with improved renal function during terlipressin therapy had a significantly higher probability for survival.<sup>87</sup> These data<sup>86,87</sup> indicate that treatment with terlipressin should be initiated as early as possible.

### *Other compounds*

Other investigational compounds to treat HRS type I, such as noradrenalin, N-acetylcystein, and a combination of albumin, octreotide and midodrine, are investigated only in small open label studies and case reports.<sup>89–91</sup> Thus, more and controlled studies with these compounds are needed before any conclusion on their efficacy in the treatment of HRS can be drawn.

*Treatment of hepatorenal syndrome (HRS) with vasoactive compounds: conclusion***Practice points**

- HRS is a serious complication in patients with cirrhosis and ascites. HRS is associated with poor prognosis unless liver transplantation can be performed.<sup>15,66,67</sup>
- Patients with HRS type I are reported to have a median survival time of less than 2 weeks and are in great need of a medication to reverse their functional renal failure and, thus, to improve survival and overall clinical outcome.<sup>66</sup>
- The most prominent circulatory deficiencies in patients with HRS comprise portal hypertension and splanchnic arterial vasodilation, leading to decreased centrally effective blood volume. Central hypovolaemia activates sodium- and volume-retaining neurohumoral systems, i.e. RAAS and SNS, thus, increasing renal sodium and water retention – as the main course for accumulation of ascites and for further deterioration of renal function (Figures 1–3).
- Terlipressin represents the most widely studied medication in this condition to-date and has shown promising activity in several clinical investigations including double-blind randomized placebo-controlled trials.<sup>63,64,69,70,74–80,83–87</sup>
- Due to its vasoconstrictory effects on the dilated splanchnic blood vessels, terlipressin moves excess blood from the splanchnic vascular compartment to the central and arterial vascular compartment. As a consequence, treatment with terlipressin refills the central arteries, reduces the vasoconstrictive activity of the RAAS and the SNS and, thus, restores blood supply to life essential organs, including liver and kidneys, potentially translating into a better organ perfusion and improvement of survival.<sup>63,69,70,80,83,84,87</sup>
- Terlipressin treatment of patients with HRS was shown to extend life until liver transplantation can be performed.<sup>15,69,83–85,87</sup>
- The earlier treatment with terlipressin starts the higher is the probability for treatment success and for survival.<sup>86,87</sup>

**Research agenda**

- More research is warranted on the optimal treatment dose and optimal length of treatment of HRS type I with terlipressin.
- Based on the observation that less severe disease in patients with HRS type I seems to provide the best chance for HRS-reversal, more research is warranted on the possible benefit of treatment with terlipressin as early as possible.
- Based on the observation that patients with pre-transplant renal dysfunction seem to have a poorer prognosis after liver transplantation than patients with normal pre-transplant renal function, more research is warranted on the effect of terlipressin treatment of cirrhotic patients with renal dysfunction before liver transplantation.

## OVERALL CONCLUSION

Bleeding of oesophageal varices and hepatorenal syndrome type I are two of the most dramatic complications in gastroenterology and have a high mortality rate. Early treatment with vasoactive drugs can save life, when skilled endoscopists are not immediately available. In contrast to the long acting vasopressin analogue terlipressin, where efficacy and mechanisms of action to arrest haemorrhage and to improve the disturbed cardiovascular situation of cirrhotic patients are well documented, those for somatostatin and octreotide remain unclear and uncertain.

Through vasoconstriction terlipressin reduces blood flow into the portal vein and, thus, reduces portal venous pressure and blood flow through porto-systemic shunts. As a consequence, variceal bleeding is arrested, central and arterial hypovolaemia is corrected and activation of the RAAS and SNS is reduced, leading to lower intrahepatic and intrarenal resistance. The result is an improvement of

- (1) organ perfusion – especially of the kidneys and the liver –
- (2) the hyperdynamic cardiovascular situation and
- (3) the survival rate.

Octreotide was shown to lower portal and mesenteric blood flow and to elevate splanchnic vascular resistance in healthy subjects. However, in patients with portal hypertension and variceal bleeding, haemodynamic effects of octreotide remain unclear. Haemodynamic effects of somatostatin on portal vessels, on collateral porto-systemic shunts and on oesophageal varices were shown to last only from a few seconds to a few minutes. Whereas terlipressin has been shown to stimulate kidney function and to prolong survival time in patients with bleeding oesophageal varices and in patients with hepatorenal syndrome, no such promising effects were observed with somatostatin or octreotide.

In consequence, terlipressin should be favoured as first choice treatment of patients with bleeding oesophageal varices in an emergency state and as adjuvant therapy to endoscopic treatments. Terlipressin has been shown to arrest bleeding and is the only medication which has been shown to increase survival time in patients with bleeding oesophageal varices.

In addition, terlipressin has been shown to improve kidney function and to reverse hepatorenal syndrome. Terlipressin has been shown to increase survival time in patients with hepatorenal syndrome and it may bridge the time until liver transplantation can be performed. The earlier treatment with terlipressin is started the higher is the probability of treatment success and survival.

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