LIVER DISEASE

Inducible nitric oxide synthase activity contributes to the regulation of peripheral vascular tone in patients with cirrhosis and ascites

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Background: Overexpression of inducible nitric oxide synthase (iNOS) and increased nitric oxide generation may be associated with the hyperdynamic circulation of patients with cirrhosis. We have, for the first time, used the highly selective iNOS inhibitor, 1400W, to determine whether iNOS activity contributes to the regulation of vascular tone in patients with cirrhosis and ascites.

Methods: Bilateral forearm blood flow was measured using strain gauge plethysmography in eight patients with cirrhosis and ascites, and eight matched healthy volunteers during intrabrachial infusion of 1400W (0.1–1 μmol/min), N^G-monomethyl-L-arginine (L-NMMA, a non-selective NOS inhibitor; 2–8 μmol), and norepinephrine (a control vasoconstrictor; 60–480 pmol/min).

Results: In patients with cirrhosis, 1400W, L-NMMA, and norepinephrine caused dose dependent reductions in forearm blood flow: peak reductions of 11 (5)%, 37 (4)%, and 48 (5)%, respectively ($p < 0.05$ for all). In contrast, 1400W had no effect on blood flow (+4 (8)%; NS) in healthy controls despite similar reductions in blood flow with L-NMMA and norepinephrine (39 (5)% and 49 (5)%, respectively; $p < 0.05$ for both).

Conclusions: We have, for the first time, demonstrated that 1400W causes peripheral vasoconstriction in patients with cirrhosis but not healthy matched controls. This suggests that iNOS contributes to the regulation of peripheral vascular tone in patients with cirrhosis and ascites, and may contribute towards the hyperdynamic circulation associated with this condition.

Patients with advanced liver disease have a hyperdynamic circulation that is characterised by low arterial pressure, high cardiac output, splanchnic vasodilatation, and low systemic vascular resistance.[1–3] This occurs despite activation of endogenous vasoconstrictor systems, and increased activity of endogenous vasodilators, such as nitric oxide,[4] has been suggested as a possible cause. Plasma concentrations of nitric oxide and its metabolites nitrite and nitrate are increased in patients with cirrhosis and ascites.[5 6] Exhaled breath of patients contains higher nitric oxide concentrations than normal subjects, and correlates with cardiac output and Child-Pugh score.[7] Moreover, systemic administration of a non-selective nitric oxide synthase inhibitor increases systemic vascular resistance and blood pressure in patients with cirrhosis.[8]

Nitric oxide is generated from L-arginine, a reaction catalysed by nitric oxide synthase (NOS). Three isoforms of NOS have been identified; endothelial, inducible, and neuronal.[9] Endothelial nitric oxide synthase (eNOS) is expressed constitutively, and produces small amounts of nitric oxide for short periods of time in response to exogenous and endogenous stimuli. It is found in a number of cell types but principally endothelial cells.[10] In contrast, inducible nitric oxide synthase (iNOS) is synthesised de novo in response to inflammation and is found in vascular smooth muscle cells, hepatocytes, macrophages, and many other cell types.[9] Once expressed, it produces large amounts of nitric oxide for prolonged periods.[9]

In various pathological states, endotoxins, cytokines, and bacterial infections have promoted iNOS formation and are associated with overproduction of nitric oxide. This causes hyporesponsiveness to vasoconstrictors and a hyperdynamic circulation.[1 2] Bacterial overgrowth and failure of the gut mucosal barrier commonly promotes bacterial translocation

and endotoxaemia in patients with cirrhosis,[11–13] and several reports have demonstrated an association between nitric oxide release and endotoxinaemia.[5 14 15] Vallance and Moncada hypothesised that, through such mechanisms, iNOS formation may account for the hyperdynamic circulation of patients with advanced liver disease.[16]

Until recently, it has not been possible to distinguish clearly between endothelial and inducible NOS activity due to the lack of specific inhibitors. N-(3-(aminomethyl) benzyl) acetamidine (1400W) is a novel selective inhibitor of human iNOS that has recently become available for clinical use.[17] It competes with L-arginine to bind irreversibly with iNOS and is at least 5000-fold more selective for iNOS than eNOS, making it one of the most selective iNOS inhibitor to date.[17] Therefore, the aim of the present study was to assess the contribution of functional iNOS activity to peripheral vascular tone in patients with cirrhosis and ascites by determining the effect of direct local intra-arterial 1400W on peripheral blood flow.

METHODS

Study population

Eight patients with biopsy proven cirrhosis, ascites, and portal hypertension, and eight age and sex matched healthy subjects were recruited. All patients were ambulant, had endoscopically proven varices, and normal serum creatinine (<100 μmol/l). In order to avoid alcohol induced depression of vascular responses,[18] patients were abstinent from alcohol for at least one month, confirmed by history and repeated blood ethanol testing. Patients with primary biliary cirrhosis

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Abbreviations: NOS, nitric oxide synthase; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; L-NMMA, N^G-monomethyl-L-arginine
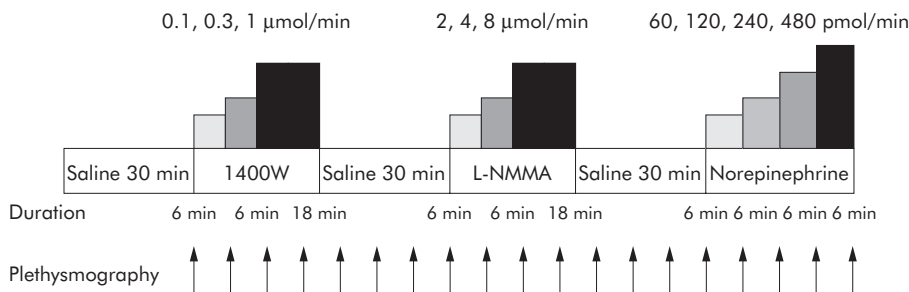
0.1, 0.3, 1 µmol/min   2, 4, 8 µmol/min   60, 120, 240, 480 pmol/min

Figure 1 Study protocol. L-NMMA, N^G-monomethyl-L-arginine.

| Saline 30 min | 1400W | Saline 30 min | L-NMMA | Saline 30 min | Norepinephrine |

Duration: 6 min   6 min   18 min   6 min   6 min   18 min   6 min 6 min 6 min 6 min

Plethysmography

were excluded due to the possible vasoactive effects of hyperbilirubinaemia. Patients with clinically overt bacterial infection, neutrophilia, or pyrexia (body temperature >37.5°C) were excluded from the study. To avoid the possibility of altering the endogenous vasopressor systems, all subjects were maintained on their normal sodium intake (~150 mmol/day). None of the patients received vasoactive (including beta adrenoreceptor blockers) or non-steroidal anti-inflammatory drugs in the week before, and all patients abstained from food, tobacco, and caffeine containing drinks for at least four hours before each study. All female subjects were postmenopausal both for safety and to avoid the variability in vascular responses that may be associated with cyclical hormonal changes.[19] The studies were undertaken in accordance with the Declaration of Helsinki of the World Medical Association, the approval of the local research ethics committee, and the written informed consent of each subject.

Drugs and intra-arterial administration

The brachial artery of the non-dominant arm was cannulated with a 27 standard wire gauge steel needle (Cooper's Needle Works Ltd, Birmingham, UK) under local anaesthesia. The cannula was attached to a 16 gauge epidural catheter (Portex Ltd, Hythe, Kent, UK) and patency was maintained by infusion of saline (0.9%: Baxter Health Care Ltd, Thetford, UK) via an IVAC P1000 syringe pump (IVAC Ltd, Basingstoke, UK). The rate of intra-arterial infusions was maintained constant throughout all studies at 1 ml/min. Pharmaceutical grade 1400W (Merck Biosciences AG, Läufelfingen, Switzerland), L-NMMA (Merck Biosciences AG), and norepinephrine (Levophed, Sanofi-Winthrop Ltd,

Guildford, UK) were dissolved in saline on the day of the study.

Haemodynamic measurements

Blood flow was measured in both forearms by venous occlusion plethysmography, as described previously.[20] Blood pressure and heart rate were monitored in the non-infused arm at intervals throughout each study with a semi automated non-invasive oscillometric sphygmomanometer.

Study design

Subjects attended on a single occasion, at 9am, and were recumbent throughout the study. Strain gauges and cuffs were applied, and the brachial artery of the non-dominant arm was cannulated. Forearm blood flow was measured every 6–10 minutes. Following a 30 minute equilibration period, during which saline was infused, subjects received intra-arterial infusions of 1400W (iNOS inhibitor) at 0.1, 0.3, and 1 µmol/min for 6–18 minutes at each dose, L-NMMA (non-selective NOS inhibitor) at 2, 4, and 8 µmol/min for 6–18 minutes at each dose,[21] and norepinephrine (control vasoconstrictor) at 60, 120, 240, and 480 pmol/min for six minutes at each dose,[22 23] with 30 minute saline washout periods between each drug infusion (fig 1).

Data analysis and statistics

Plethysmographic data were extracted from chart data files, and the last five linear recordings in each measurement period were averaged. Forearm blood flows were calculated from the plethysmographic data, as described previously.[20]

Table 1 Patient and subject characteristics

Variable	Patient with cirrhosis (n = 8)	Healthy controls (n = 8)
Age (y)	58 (2)	59 (3)
Sex (M:F)	7:1	7:1
Aetiology of liver disease:		
Alcoholic	8	–
Child Pugh Score	9 (1)	–
Child Grade		
A	1	
B	3	–
C	4	–
Serum albumin (g/l)	32 (3)	–
Serum bilirubin (mmol/l)	46 (9)	–
Serum creatinine (µmol/l)	82 (6)	
Prothrombin time (s)	14 (1)	–
Oesophageal varices	8	–
Ascites	8	–
Baseline blood pressure		
Systolic (mm Hg)	138 (5)	143 (6)
Diastolic (mm Hg)	76 (4)	81 (3)
Baseline heart rate (/min)	89 (4)	59 (3)*
Resting forearm blood flow (ml/100 ml tissue/min)	2.4 (0.3)	2.1 (0.1)

Results are expressed as mean (SEM).
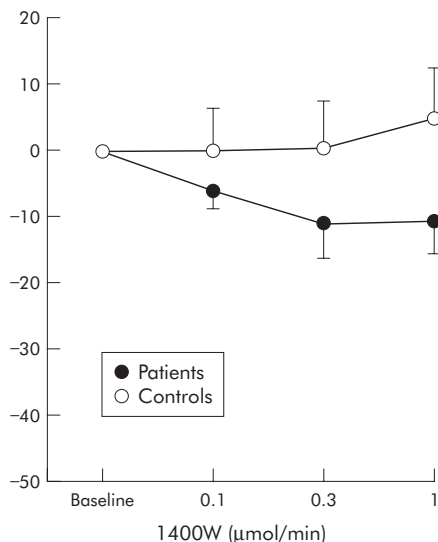*p<0.05 versus controls.

Figure 2 Percentage change in forearm blood flow after infusion of the inducible nitric oxide synthase inhibitor 1400W in patients and healthy controls.

Figure 3 Percentage change in forearm blood flow after infusion of the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA) in patients and healthy controls.

Data were examined, where appropriate, by ANOVA with repeated measures and two tailed Student's t test using Microsoft Excel 2002. Data are expressed as mean (SEM). Statistical significance was taken at the 5% level.

RESULTS

Patients with cirrhosis were well matched to control subjects (table 1) although patients had a higher heart rate, in keeping with their hyperdynamic circulation. Throughout each study, there were no significant changes in mean arterial pressure, heart rate, or forearm blood flow in the non-infused arm. There was no significant difference in baseline forearm blood flow in the infused arm between patients with cirrhosis and control subjects (3.9 (0.7) and 3.9 (0.7) ml/100 ml/min, respectively).

In patients with cirrhosis, intrabrachial infusion of 1400W, L-NMMA, and norepinephrine caused dose dependent reductions in infused forearm blood flow: peak reductions of 11 (5)%, 37 (4)%, and 48 (5)%, respectively (p<0.05 for all). In contrast, 1400W had no effect on blood flow (+4 (8)%; NS) in healthy controls despite similar reductions in blood flow with L-NMMA and norepinephrine (39 (5)% and 49 (5)% respectively; p<0.05 for both) (figs 2–4; table 2).

DISCUSSION

We have, for the first time, demonstrated that inhibition of inducible NOS causes vasoconstriction in the forearm circulation of patients with cirrhosis due to alcoholic liver disease. This finding suggests that inducible NOS may be partly responsible for the overproduction of nitric oxide associated with the hyperdynamic circulation of cirrhosis.

In 1991, Vallance and Moncada[16] suggested that the characteristic hyperdynamic circulation of liver cirrhosis resulted from increased production of nitric oxide secondary to endotoxaemia induced expression of iNOS. Both animal[24–27] and clinical[28] studies have variably provided support for this hypothesis, with significant tissue expression of iNOS in cirrhosis. However, current opinion suggests that eNOS rather than iNOS is the isoform responsible for the circulatory dysfunction associated with cirrhosis.[26 27] The majority of the data supporting a role for eNOS comes from rodent models without advanced liver disease. In a rodent model of cirrhosis with advanced liver disease, clear
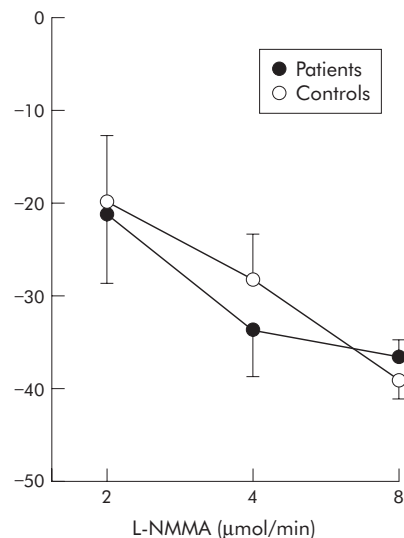
induction of iNOS was demonstrated in the splanchnic vasculature.[29] This suggests that differing isoforms of NOS may play varying roles through the course of cirrhosis, with eNOS the dominant isoform in early cirrhosis and iNOS the dominant isoform in advanced cirrhosis. For the first time, our data suggest that iNOS appears to be functionally active and may contribute to the regulation of vascular tone in patients with cirrhosis and ascites.

During our study and in previous work,[21 23 30] infusion of the non-selective NOS inhibitor, L-NMMA, produced a similar vasoconstriction in healthy controls and patients with cirrhosis. This suggests that if overall NOS activity is similar, then the contribution from eNOS must be down-regulated. Indeed, decreased eNOS expression and increased iNOS expression occurs in other inflammatory conditions[31–33] and is consistent with our findings in patients with cirrhosis.

The forearm circulation is generally representative of other systemic vascular resistance beds.[34] In the present clinical study, we have not established the role of iNOS in the
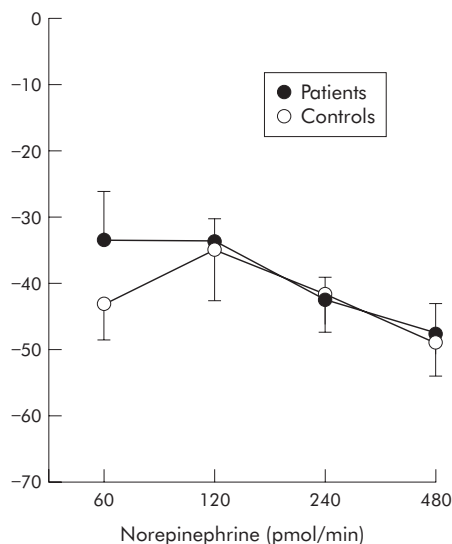

Figure 4 Percentage change in forearm blood flow after norepinephrine infusion in patients and healthy controls.

Table 2 Forearm blood flow responses in patients and healthy controls

	Patients with cirrhosis	Healthy controls
1400W (µmol/min)		
0.1	−7 (4)	0 (7)
0.3	−11 (5)*	0 (7)
1	−11 (5)*	4 (8)
L-NMMA (µmol/min)		
2	−21 (6)	−20 (7)
4	−34 (4)	−29 (5)
8	−35 (5)	−39 (4)
Norepinephrine (pmol/min)		
60	−34 (7)	−43 (5)
120	−34 (4)	−35 (7)
240	−43 (3)	−42 (5)
480	−48 (5)	−49 (5)

Results are mean (SEM).
*p<0.05 versus controls.

splanchnic or portal circulations of patients with cirrhosis. However, if the forearm circulation is a valid surrogate, then selective iNOS inhibition would be expected to improve the portal hypertension and systemic hypotension associated with cirrhosis. We therefore believe that systemic studies are needed to assess the role of iNOS inhibition in patients with cirrhosis and portal hypertension.

Study limitations

The present study is the first to use the iNOS inhibitor 1400W in humans in vivo. 1400W is a monoamidine monoamine analogue that competes with L-arginine to bind tightly and irreversibly to iNOS. It is more than 5000-fold more potent against purified human iNOS than eNOS and is one of the most selective inhibitors of iNOS reported to date.[17] The selectivity of 1400W, both in vitro and in vivo, makes it an attractive tool for assessing the contribution of iNOS. However, an important concern is whether the dose of 1400W chosen is appropriate to achieve complete inhibition of iNOS activity in vivo. 1400W inhibits rodent vascular iNOS with an EC_{50} value of 0.8 µM, an eightfold higher potency than L-NMMA which inhibits iNOS with an EC_{50} value of 6 µM.[35] During infusion of 1400W at 1 µmol/min, with calculated blood flow rates of approximately 20–25 ml/min, we would predict effective end organ concentrations to be between 40 and 50 µM—that is, more than 50-fold higher than the EC_{50}. We are therefore confident that we have achieved complete and selective iNOS inhibition in our study. During the study, forearm blood flow did not return to baseline after infusion of 1400W in patients with cirrhosis. This is not unexpected as 1400W is an irreversible inhibitor of iNOS[17] and why we designed the study with 1400W as the first infusion.

Another potential limitation is that all patients had alcohol induced liver disease and our findings may not be applicable to other forms of liver cirrhosis. Excess alcohol intake is known to alter the response to exogenous vasopressor agents, such as norepinephrine.[18] However, all our subjects were abstinent from alcohol for a minimum of one month, as determined by clinical history and random ethanol testing. Moreover, consistent with previous work,[22 23] we have demonstrated a normal response to norepinephrine infusion, suggesting no significant derangements in vascular smooth muscle function.

In conclusion, we have, for the first time, demonstrated that 1400W causes peripheral vasoconstriction in patients with cirrhosis but not in healthy matched controls. This suggests that iNOS contributes to the regulation of peripheral vascular tone in patients with cirrhosis and ascites, and may contribute towards the hyperdynamic circulation associated with this condition. Further studies are required to look at the role of iNOS in differing stages of cirrhosis and in patients with advanced cirrhosis undergoing bacterial decontamination.

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EDITOR'S QUIZ: GI SNAPSHOT ....

Answer

From question on page 541

Computed tomography (CT) scan showed invagination of a segment of thickened terminal ileum into the ascending colon at the level of the hepatic flexure. The leading point of the intussusceptum revealed marked mucosal irregularity and created a convex margin as it met air in the distended ascending colon. Laparotomy was performed and revealed an 8 cm bowel mass with telescoping of the terminal ileum to the ascending colon. Right hemicolectomy without reduction of intussusception and primary anastomosis was performed. The operative specimen demonstrated the leading point of the intussusception as a circumferential ulcerative caecal tumour (fig 2). The patient recovered well and was discharged eight days after operation. Pathology revealed Dukes' C moderately differentiated adenocarcinoma.

Enteric intussusception is an uncommon condition in adults. It represents 1% of patients with bowel obstructions. In contrast with intussusception in children, a demonstrable aetiology is found in 70–90% of cases, of which at least half are due to malignancy. The lesion disturbs peristalsis of the bowel and causes telescoping of the proximal segment into the distal bowel lumen. Unlike the acute presentation in children, adult intussusception may present with acute, intermittent, or chronic symptoms. Abdominal pain is the most common presentation. CT usually shows the intussusception complex well. Other investigations may include ultrasound, contrast study, or colonoscopy. Treatment requires resection of the involved segment of bowel with its draining lymphatic due to the high likelihood of an underlying malignancy. Reduction should be avoided as the bowel
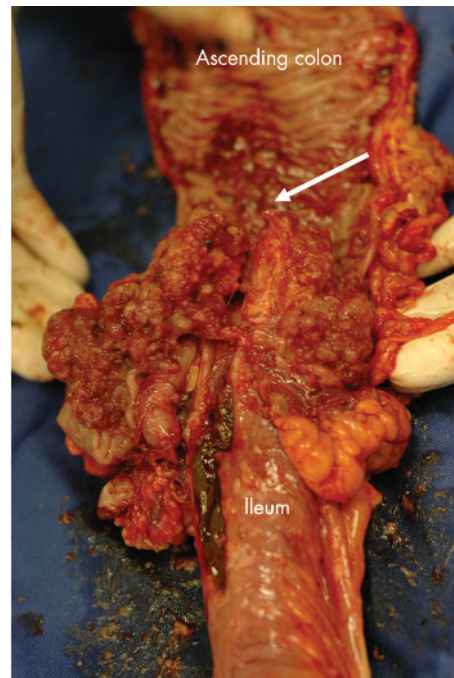

Figure 2 Operative specimen demonstrated the leading point of the intussusception as a circumferential ulcerative caecal tumour.

wall involved is usually oedematous and friable. Manipulation increases the risk of bowel perforation, contamination, and possible cancer spillage.