Cardiac response to exercise in cirrhosis

Reading the excellent article on the cardiac response to exercise in cirrhosis (Gut 2001;49:268–75), I was surprised that patients without ascites were labelled “preascitic”. The implication is that these patients have not yet developed ascites, presumably because their disease is less advanced than in those patients with ascites. It is well known that many patients with cirrhosis will never develop ascites, regardless of the severity of other sequelae of portal hypertension that have developed or will ultimately develop. This is certainly borne out by my experience at a busy liver transplant centre. I would respectfully suggest that these patients be instead called simply “cirrhotic patients without ascites”.

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Authors’ reply

We thank Dr Wachsberg for his comments and apologise for not making ourselves clear. In contrast with cirrhotic patients without ascites, who may well have had ascites and used diuretics sometime in the past, preascites is a well characterised stage in the natural history of cirrhosis. It occurs early in the continuum of cirrhosis. Such patients have never had ascites nor required the use of diuretics, and yet they show evidence of abnormal renal handling of sodium. They maintain sodium balance while on a diet of 100 mmol/day sodium but retain sodium when given an acute sodium load such as 200 mmol/day sodium for one week.1 However, these patients can eventually come to sodium balance, after an intake of 200 mmol/day sodium but at the expense of an increase in total and central blood volume, together with suppression of renin-angiotensin-aldosterone and sympathetic activities in the supine position.2 The assumption of the erect posture leads to activation of these hormonal systems which are responsible for the subtle sodium retention in these patients. Preascites is further characterised by increased dopaminergic activity,3 a possible consequence of the expanded intravascular volume, and elevated nitric oxide levels,4 which partly contributes to the glomerular hyperfiltration observed in these patients.5 Finally, preascitic patients also have increased muscle sympathetic nervous activity6 although the significance of this is not clear at present. Thus the preascitic cirrhotic patient is not simply a cirrhotic patient without ascites but rather the syndrome of preascites is a syndrome with well defined characteristics. While many patients in Dr Wachsberg’s busy liver transplant unit may not have ascites, and they may well be receiving their liver transplant for reasons other than ascites, they certainly cannot be confused with preascitic cirrhotic patients.

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References


Aetiology of extrahepatic portal vein thrombosis

I read with interest the article by Janssen et al (Gut 2001;49:720–4) regarding the aetiology and determinants of survival of extrahepatic portal vein thrombosis (EPVT). Among others, this retrospective study investigated the systemic risk factors for EPVT. We would like to add hyperhomocysteinemia as a relatively new, not yet mentioned, risk factor.10 This is illustrated by a recent case in our clinic. A 54 year old woman was hospitalised because of worsening of upper abdominal pain which started two weeks before admission and was continuously present. Her personal and family history for thromboembolic processes was uneventful and she did not smoke. She did not use vitamin supplements. One day prior to admission she was...
using the progesterone norethisterone (Primolut N) because of vaginal blood loss.

Combined portal-splenic vein thrombosis was diagnosed using colour Doppler ultrasonography and computed tomography. There were already some venous collaterals in the hilar area of the liver; hence the thrombosis would have been present for at least several weeks.

After investigations for thrombophilias were carried out, intravenous heparin and oral anticoagulant therapy were started and the patient improved.

The patient was found to be heterozygous for the prothrombin gene G20210A mutation and for the methyltetrahydrofolate reductase gene mutation. Mild hyperhomaocysteaemia (fasting/six hour post methionine load values 18.91 µmol/l) was also detected. Plasma vitammin B12, B6, and folate levels were normal. The patient is currently on lifelong oral anticoagulant therapy and has not yet started to use vitamin supplements.

Mild hyperhomocysteaemia is a hypercoagulability risk factor for the development of portal vein thrombosis. At the time of the start of his therapy, Spanier et al., had not been recognised as a prothrombotic factor. The association of hyperhomaocysteaemia and prothrombin gene mutation in EPVT has been documented only recently in the literature. It is still unclear if the association is additive or synergistic for the development of thrombosis. We would like to recommend determination of homocysteine levels in patients with idiopathic EPVT as vitamin B6 and folate supplementation is a cheap and safe therapy in preventing deleterious vascular complications.

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References

Author’s reply

Spanier and Frederiks describe the role of diagnosing hyperhomocysteaemia in a patient with portal vein thrombosis. Their case not only illustrates the potential importance of hyperhomocysteaemia but also the concurrence of multiple risk factors in portal vein thrombosis. Two inherited thrombotic risk factors (methyleneheterohydrofolate and prothrombin gene G20210A mutation) predisposed the patient to a thrombotic event which became clinically manifest after the recent start of progesterone.

It is already evident that hyperhomocysteaemia is an independent risk factor for cardiovascular diseases. Hyperhomaocysteaemia can be diagnosed by genetic testing for the methyleneheterohydrofolate mutation and by measurement of increased plasma homocysteine levels, both fasting and after loading with methionine. The pathophysiological mechanism of homocysteine induced vascular disease is not well understood. It is even unclear whether homocysteine itself or a related metabolite or cofactor is primarily responsible for the thrombogenic effects of hyperhomocysteaemia.

In our study on risk factors and determinants of survival for portal vein thrombosis, we did not investigate hyperhomocysteaemia as a risk factor. As mentioned by Spanier and Frederiks, this relates primarily to the fact that in most of our patients hyperhomocysteaemia was not recognised as an established thrombogenic risk factor at the time of diagnosis. Furthermore, we did not consider comorbidity or concurrent risk factors for portal vein thrombosis, which may lead to poor nutritional status and therefore interfere with plasma homocysteine measurement. These factors include the presence of liver cirrhosis, malignancy, and infections. Although testing for the point mutation (C677T) in the methylenetherythromethaftolate reductase gene is an important factor for the prothrombotic disease, we did not study this in our patients. As mentioned by Spanier and Frederiks, the association of hyperhomaocysteaemia and prothrombin gene mutation in EPVT has been documented only recently in the literature. It is still unclear if the association is additive or synergistic for the development of thrombosis. We would like to recommend determination of homocysteine levels in patients with idiopathic EPVT as vitamin B6 and folate supplementation is a cheap and safe therapy in preventing deleterious vascular complications.

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References

Rifampicin and treatment of cholestatic pruritus
Prince et al described three patients with primary biliary cirrhosis who developed hepatocholestatic pruritus when given rifampicin to treat their cholestatic pruritus (Gut 2001; 50:436–9). They describe the use of rifampicin as “secondline” treatment of cholestatic pruritus. Firstline therapy is generally considered to be cholestyramine, a bile acid sequesterant. Use of this agent is frequently limited because of gastrointestinal side effects, especially constipation. I am writing to summarise new evidence that retention of endogenous bile acids causes cholestatic pruritus, and to call attention to a recent abstract indicating that cholestyramine, a new bile acid sequestrant, appears to be more potent than cholestyramine and does not induce constipation.

The view that bile acid retention causes cholestatic pruritus is a very old one. Varco et al in 1947 noted that biliary drainage reduced pruritus in patients with extrahepatic biliary obstruction and that when bile was fed to patients, their pruritus returned. Huet and colleagues reported that biliary drainage improved cholestatic pruritus in patients with intrahepatic cholestasis. Administration of cholestyramine, an anion exchange resin with affinity for bile acids, improved pruritus as did passage of plasma over charcoal or anion exchange resins. More recently, extracorporeal biliary bypass and direct reabsorption of bile acids, has been shown to diminish cholestatic pruritus. In all of these procedures, retained substances in addition to bile acids could have been removed at the same time so that cause and effect relationships were uncertain.

Partial biliary diversion is effective in treating cholestatic pruritus. A likely explanation for the efficacy of this surgical procedure is that it reduces the load of bile acids on the transport system and thence to the liver, resulting in less retention of bile acids. In an important study, Hollands et al reported that ideal biliary bypass was effective in reducing cholestatic pruritus. The ideal transport system is considered to solely transport bile acids. Thus this report in the surgical literature provided unequivocal evidence for bile acids being related directly or indirectly to cholestatic pruritus.

If bile acids are causal agents, and if bile acid depletion improves cholestatic pruritus, then bile acid administration to cholestatic patients should induce pruritus. Prince et al reported that in two of four patients with primary biliary cirrhosis given cholestyramine, a non-metabolisable conjugated bile acid analogue, pruritus was induced.

Despite these convincing lines of evidence, recent authors have been sceptical of the role of bile acids in cholestatic pruritus. This scepticism has arisen because of the lack of correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies. However, in my opinion, the lack of correlation between plasma bile acid levels and pruritus does not exclude a causal role for bile acids for three reasons. Firstly, the plasma bile acids fluctuates diurnally and the correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies. However, in my opinion, the lack of correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies. However, in my opinion, the lack of correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies. However, in my opinion, the lack of correlation between plasma bile acid levels and the magnitude of pruritus in some, but not all, studies.
bile acid binding is relatively weak. Thus the ileal transport system for bile acids acts as a sink to strip the bound bile acids from the resin. A new bile acid binding polymer, colesevalem, was synthesised by GelT ex Pharmaresin. A new bile acid binding polymer, bile acid binding is relatively weak. Thus the 6-hydroxylation. did not note that rifampicin has a striking intestinal side effects. additional advantage over cholestyramine in in combination, on cholestatic pruritus. and convenience of these two agents, alone or al

**References**


**Oats and coeliac disease**

We read the study by Janatuinen et al (Gut 2002; 50:332–5) with great interest. However, we would like to highlight some concerns.

The initial study randomly assigned patients randomised to two groups—oats and gluten free diet, 45 and 47 patients respectively—however, these numbers do not correspond to those in figure 1 of their paper. Patients were verbally consenting volunteers, thus introducing selection bias to compliance. The number of dropouts, especially in the control group, was surprisingly high (41 out of 47). There were several dropouts because of the long term safety of oats or concerns over their safety? If the latter, then surely this would be greater in the oats group.

It is not clear whether patients were followed up in the same period between 12 months and five years. It would be important to ascertain objectively whether the oats group were in fact including oats in their diet, as omission would not address their long term safety. Assessment of compliance and food diary are very subjective, introducing bias towards dietary compliance. How was this done? We were surprised to see that one third of the oats group did not in fact take oats at all, so only seven of 19 patients were ingesting oats on a daily basis. The proportion adhering to a gluten free diet was paradoxically greater in the control group. If oats were allowed then this could be interpreted by patients as acceptance of other (gluten containing) foods also. The purity and amount of oats ingested in the first year was regulated from major Finnish mills. These products have been well tolerated. In our opinion this does not justify such a conclusion. As stated in the article, the oats group also consumed a strict gluten free diet but part of their gluten free products were substituted by oats.

After 12 months, patients used oat products from major Finnish mills. The oats had not been tested to be free of contamination. If oats by itself or oat products had any deteriorating effect on the duodenal mucosa or stimulated immune mechanisms, the results in the oats group would have differed from those of controls. This was not the case. The results indicate that oats were well tolerated.

As in our original study (Gut 2002; 50:332–5), histological examination of the small bowel was performed on all study patients in the oats group. As stated in the article, patients had free choice regarding the amount of oats they wished to consume and which they felt convenient. In respect the study also depends on the reality and usefulness of oat products. Information on the quantity of oats ingested in the diet and the degree of compliance was based on an interview and a questionnaire carried out by a clinical nurse.

Dor and Shanahan raise the question of whether patients interpreted the use of oats as comparable with consuming gluten containing foods. They base this on the degree of compliance in our study. Compliance was 71.4% in the oats group and 78.6% among controls. In our opinion this does not justify such a conclusion. As stated in the article, the oats group also consumed a strict gluten free diet but part of their gluten free products were substituted by oats.

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supplements, would be an enormous effort. To date, our investigation is the largest controlled randomised study on oats in coeliac patients. Furthermore, it represents the first attempt in showing the long term safety of oats in coeliac patients.

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Reference

NOTICES

Sir Francis Avery Jones BSG Research Award 2003

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:

• A manuscript (2 A4 pages ONLY) describing the work conducted
• A bibliography of relevant personal publications
• An outline of the proposed content of the lecture, including title
• A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

Broad Medical Research Program—Inflammatory Bowel Disease Grants

Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L. Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no substance) deadline: June 1. A rapid application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

3rd Nutrition and Health Conference

This will be held on 29–30 November 2002 in London, UK. This year’s topics include cancer prevention, cancer treatment, hot topics in coronary heart disease and diet, brain nutrition, gut nutrition, and a diet and lifestyle intervention session. Further information: Nutrition and Health Conference, 16 Brownlow Court, Lyttleton Road, London N2 5RF; tel: +44 (0)208 455 6570; fax: +44 (0)208 455 2146; email: admin@nutritionandhealth.co.uk; website: www.nutritionandhealth.co.uk

17th International Workshop on Therapeutic Endoscopy

This will be held on 3–5 December 2002 in Hong Kong. Further information: Professor SC Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong. Tel: +852 2632 2233; fax: +852 2635 0075; email: info@hksde.org

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: wwww.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy

This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.

The Future of Gastro-entero-hepato-pancreatology is bright

This Academic Farewell Symposium of Guido NJ Tytgat will be held on 12 December 2002 in Amsterdam, the Netherlands. Deadline for registration is 1 November 2002 (no registration fee) and registration should be done via email to: goedkop@amc.uva.nl.

Cancer of Oesophagus and Gastric Cardia: from Gene to Cure

This conference will be held on 13–15 December 2002 in Amsterdam, The Netherlands. Further information: European Cancer Centre, PO Box 9236, NL 1006 AE Amsterdam, The Netherlands. Tel: +31 (0)20 346 2547; fax: +31 (0)20 346 2523; email: ecc@ikca.nl

The Sheila Sherlock Memorial Symposium

Dame Sheila Sherlock, who died earlier this year, was responsible for creating hepatology at the Royal Free Hospital, London. This memorial symposium will take place on 26–28 January 2003 at the Royal Free Hospital, London. Further information: Terri Dolan, Royal Free and University College Medical School, Royal Free Campus, Centre for Hepatology, Upper 3rd Floor, Rowland Hill Street, London NW3 3PF, UK. Tel: +44 (0)207 433 2891; email: t.dolan@rfc.ucl.ac.uk

3rd Chester International Inflammatory Bowel Disease Meeting

This meeting will be held on 10–11 February 2003 in Chester, UK. An international programme includes speakers from the USA, France, Italy, and the UK, and will cover clinical problems, pathogenesis, medical and surgical treatment. Registration details and programme from: Professor Jonathan Rhodes, Department of Medicine, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesjn@liverpool.ac.uk