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 as 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. 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. 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, a possible consequence of the expanded intravascular volume, and elevated urinary sodium excretion levels, which only partly contributes to the glomerular hyperfiltration observed in these patients. Finally, preascitic patients also have increased muscle sympathetic nervous activity 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. 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 ultrasoundography 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 methylenetetrahydrofolate reductase (MTHFR) C677T allele, and for the methyltetrahydrofolate reductase (MTHFR) C677T allele. Hyperhomocysteinemia (fasting/six-hour post methionine load values 18.91 mmol/l) was also detected. Plasma vitamin 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 hyperhomocysteinemia is a hypercoagulability risk factor for the development of thrombosis. At the time of the study of Janssen et al., had not been recognised as a prothrombotic factor. The association of hyperhomocysteinemia and prothrombin gene mutation in EPVT has been documented only 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 hyperhomocysteinemia in a patient with portal vein thrombosis. Their case not only illustrates the potential impact of hyperhomocysteinemia but also the concurrence of multiple risk factors in portal vein thrombosis.1 Two inherited thrombosis risk factors (methylenetetrahydrofolate and prothrombin gene G20210A mutation) predisposed the patient to a thrombotic event which became clinically manifest after the recent start of progesterone.

The clear evidence that hyperhomocysteinemia is an independent risk factor for cardiovascular diseases. Hyperhomocysteinemia can be diagnosed by genetic testing for the methylenetetrahydrofolate 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 metabolie or cofactor is primarily responsible for the thrombogenic effects of hyperhomocysteinemia.

In our study on risk factors and determinants of survival for portal vein thrombosis, we did not investigate hyperhomocysteinemia in a larger number of patients. However, the current study relates primarily to the fact that in most of our patients hyperhomocysteinemia was not recognised as an established thrombogenic risk factor at the time of diagnosis. Furthermore, we investigated somatic 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.1 Although testing for the point mutation (G677T) in the methylenetetrahydrofolate reductase gene avoids the problem of acquired hyperhomocysteinemia, this genetic defect by itself does not appear to be a significant independent risk factor for atherothrombotic disease.1 From a therapeutic viewpoint, testing for hyperhomocysteinemia is interesting, also for portal vein thrombosis, because vitamin supplementation (with folic acid, pyridoxine, and vitamin B12) is generally effective in reducing homocysteine concentrations. However, it is not known if this therapy confers a risk for either extensive splanchic thrombosis or other thrombotic manifestations which can develop in patients with portal vein thrombosis.1

We agree that it would be preferable to use the progesterone norethisterone (Primolut N) because of gastrointestinal side effects, especially constipation. I am writing to summarise new evidence that retention of endogenous bile acids causes cholestasis, and to call attention to a recent abstract indicating that colesualem, a new bile acid sequestran, appears to be more potent than cholestyramine and does not induce constipation.

This view that bile acid sequestration 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 colleagues1 reported that biliary drainage improved cholestatic pruritus in patients with intrahepatic cholestasis. Administration of cholestyramine, an anion exchange resin with specificity for bile acids, improved pruritus as did passage of plasma over charcoal or anion exchange resins.2 More recently, extracorporeal plasma exchange with specific bile acid binding columns has been shown to diminish cholestatic pruritus.1 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 to the transport system and thence to the liver, resulting in less retention of bile acids. In an important study, Hollands et al. reported that ileal bypass was effective in reducing cholestatic pruritus.3 The ileal 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 causative agents, and if bile acid depletion improves cholestatic pruritus, then bile acid administration to cholestatic patients should induce pruritus. 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 composition of plasma bile acids in cholestasis is quite complex. Secondly, bile acids might act slowly on peripheral or central receptors (or on the release of substances that act on these receptors) so there could be a long delay between elevated plasma levels and pruritus. Thirdly, endogenous molecules such as opiates could act synergistically with bile acids to induce cholestatic pruritus.

Cholestyramine binds bile acids but is frequently ineffective. The efficiency of cholestyramine binding is quite low because the Km for the ileal transport system is in the micromolar range, and at this concentration

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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, colesevelam, was synthesised by GelTex Pharmaceuticals (now Genzyme General) with a much superior binding affinity for bile acids. Colesevelam is a hydrogel that was developed as therapy for hypercholesterolaemia. Berg, in a recent abstract, reported that in eight patients with cholestatic pruritus who had not responded to cholestyramine, colesevelam was effective in five. Colesevelam has an additional advantage over cholestyramine in that colesevelam does not have gastrointestinal side effects.

In their thoughtful case report, Prince et al did not note that rifampicin has a striking effect on bile acid metabolism, inducing 6-hydroxylation. It could well be that 6-hydroxy bile acids either do not induce pruritus or are not considered by the ileal transport system, as compared with endogenous bile acids, or both. Rifampicin is presumed to induce 6-hydroxylation of bile acids via cyP3A, a microsomal enzyme, whose synthesis is induced by the interaction of rifampicin and the nuclear receptor PXR. PXR activation might also induce bile acid sulfation.

If the use of rifampicin is hazardous in cholestatic disease, as suggested by Prince et al, then management of cholestatic pruritus should involve a bile acid sequestran such as colesevelam and/or an opiate antagonist. It would seem desirable to initiate a prospective, placebo controlled, double blind study using state of the art methods for quantifying itching that would compare the efficacy, safety, and convenience of these two agents, alone or in combination, on cholestatic pruritus.

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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 randomised 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 (41)). There were so many dropouts because of either unpalatability 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 oats and control groups of 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 one third of 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 but this was not monitored thereafter and contamination of oat products could lead to small bowel architectural changes.

Histological changes in coeliac disease can be subjective but no mention was made as to whether blind reporting was carried out. It is not clear whether patients were included in the study as full blood and neutrophil counts. Histological examination of the duodenal mucosa is a well established investigation, but this was not monitored thereafter and contamination of oat products could lead to small bowel architectural changes.

The safety of oats in coeliac disease is extremely important. This and other studies have shown that compliance with a strict gluten free diet is difficult, reflecting its unacceptable profile. This paper suggests that oats are safe but the small numbers involved could mask subtle differences between the groups which may result in greater morbidity. In order to address this, further larger multicentre trials are required.

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Reference


Authors’ reply

Dor and Shanahan point out the inconsistent number in the study patients in the control group in figure 1 of the original study (Gut 2002;50:332–5) should be 1947 rather than 1949. This was an error. The number of patients in the oats group in remission in the original study (Gut 2002;50:332–5) should be 31 rather than 32 as given in the text are however correct.

Dor and Shanahan also emphasise the total number of dropouts (41) which covers both the original study of 6–12 months and the follow up the short five years. They ask whether this could be due to the possible unpalatability of oats. However, the number of dropouts was similar among controls (19) and patients consuming oats (22) and there was no evidence that the oats products were unpalatable.1 Probably the number of dropouts in many cases reflects the lack of motivation to participate, especially in the unpleasant part of the study—that is, gastroscopy to obtain small intestinal biopsy. As expressed in the text, many patients also felt uncertain about the long term safety of oats. We wished to consume and which they felt convenient. In this respect the study also depended on the reality and usefulness of oat products. Information on the quantity of oats in the diet and the degree of compliance was based on an interview and a questionnaire carried out by a clinical nurse specialist.

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 gluten containing diet but part of their gluten free products were substituted by oats.

After 12 months, patients used oat products from major Finnish mills. These products have been found 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 and usefulness of oat products. Information on the quantity of oats in the diet and the degree of compliance was based on an interview and a questionnaire carried out by a clinical nurse specialist.

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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

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 Browntown Court, Lyttleton Road, London N2 0EA; tel: +44 (0)208 455 6570; fax: +44 (0)208 455 2126; 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@hkse.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: www.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: j.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 2525; 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: Professor terril 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, Daubly Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesjn@liverpool.ac.uk