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 or when challenged with an intravenous saline 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 renin and aldosterone levels, which 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.

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 hyperhomocystinaemia 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 (Prinivil 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 methylenetetrahydrofolate reductase point mutation. Mild hyperhomocysteinaemia (fasting/six hour post methionine load values 18.91/μmol/l) was also detected. Plasma vitamin B6, B12, and folate levels were normal. The patient is currently on lifelong oral anticoagulant therapy and has not yet started to use vitamin supplements.

Mild hyperhomocysteinaemia is a hypercoagulability risk factor for the development of the first episode of the time of surgery of Janssen et al., had not been recognised as a prothrombotic factor. The association of hyperhomocysteinaemia and prothrombin gene mutation in EPVT has been documented elsewhere 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
Spanjer and Frederiks describe the role of diagnosing hyperhomocysteinaemia in a patient with portal vein thrombosis. Their case does not only illustrate the potential importance of hyperhomocysteinaemia but also the concurrence of multiple risk factors in portal vein thrombosis.‘ Two inherited thrombotic 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.

It is clear evidence that hyperhomocysteinaemia is an independent risk factor for cardiovascular diseases. Hyperhomocysteinaemia 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 metabolite or cofactor is primarily responsible for the thrombogenic effects of hyperhomocysteinaemia.

In our study on risk factors and determinants of survival for portal vein thrombosis, we did not investigate hyperhomocysteinaemia. As mentioned by Spanjer and Frederiks, this relates primarily to the fact that in most of our patients hyperhomocysteinaemia was not recognised as an established thrombogenic risk factor at the time of diagnosis. Furthermore more determinants of survival 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 methylenetetrahydrofolate reductase gene avoids the problem of acquired hyperhomocysteinaemia, this genetic defect by itself does not appear to be a significant independent risk factor for atherothrombotic disease.‘ From a therapeutic viewpoint, testing for hyperhomocysteinaemia 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.‘

Ongoing prospective controlled trials are investigating the potential beneficial effect of homocysteine lowering treatment on cardiovascular morbidity and mortality in subjects with hyperhomocysteinaemia. Before advocating widespread screening for hyperhomocysteinaemia in patients with portal vein thrombosis, it would be preferable to have a better understanding of the clinical efficacy of these therapeutic interventions.

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References

Rifampicin and treatment of cholestatic pruritus
Prince et al described three patients with primary biliary cirrhosis who developed hepato}
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 GenTex 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 be well that 6-hydroxy bile acids either do not induce pruritus or are not conserved 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 itch-pruritus.

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 design randomised 29 patients—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 in total). Were there so many dropouts because of a lack of efficacy 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 fashion 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 16 of the patients were actually consuming 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. Also, no explanation is given for the greater numbers of high values for ARA, AGA, and EMA in both groups at five years. This needs to be quantified and statistically analysed.

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 uncompromising limitations as well its relative unpalatability. 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.

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 free 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 of the duodenal biopsies showed no significant differences between the control and oats groups. The high values occurred only in a few patients in both the control and oats groups without any significant effect. As stated, those patients showed poor adherence to a gluten free diet. We do agree with the final conclusion of Dor and Shanahan that larger multicentre trials could be worthwhile. However, to conduct a similar controlled study with larger numbers of patients and continuous frequent control of intake of oats, including multinational purity analyses of freely available oat products, we would like to highlight some concerns.
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, 2 pages, double spaced, with a one-page CV) should be submitted in one week from this notice. A double spaced, single line page of data will be requested for 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 for 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 OEA; tel: +44 (0)208 435 6570; fax: +44 (0)208 435 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@hksde.org

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heath 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 2523; email: ccc@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, UK. Further information: Professor DJ 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, Daubly Street, Liverpool L69 3GA, UK, Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesj@liverpool.ac.uk