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 should be instead called simply “cirrhotic patients without ascites”.

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Authors’ reply

We thank Dr Wachberg 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 they still show evidence of abnormal renal handling of sodium. They maintain sodium balance while on a diet of 100 mmol/day sodium\(^1\) but retain sodium when given an acute sodium load such as 200 mmol/day sodium for one week\(^2\) or when challenged with an intravenous saline load.\(^3\) However, these patients can eventually come to sodium balance, after an intake of 200 mmol/day sodium\(^4\) but at the expense of an increase in total and central blood volume,\(^5\) together with suppression of renin-angiotensin-aldosterone and sympathetic activities in the supine position.\(^6\) The assumption of the erect posture leads to activation of these hormonal systems\(^7\) which are responsible for the subtle sodium retention in these patients. Preascites is further characterised by increased dopaminergic activity,\(^8\) a possible consequence of the expanded intravascular volume, and elevated urinary sodium excretion,\(^9\) which partly contributes to the glomerular hyperfiltration observed in these patients.\(^10\) Finally, preascitic patients also have increased muscle sympathetic nervous activity\(^11\) 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 Wachberg’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.\(^1\) 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 supplemments. One day prior to admission she was...
using the progesterone nor-ethisterone (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 with negative results, intraintravenous 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 methylene tetrahydrofolate reductase mutation. Mild hyperhomocysteinemia (fasting six-hour post methionine load values 18·91 μmol/l) was also detected. Plasma vitamin B12, B6, and folate levels were normal. The patient is currently on lifelong oral anticoagulation therapy and has not yet started to use vitamin supplements.

Mild hyperhomocysteinemia is a hypercoagulability risk factor for the development of portal vein thrombosis in the time of the study. Janssen et al., had not recognised as a prothrombotic factor. The association of hyperhomocysteinemia and prothrombin gene mutation in EPVPT has been documented only once 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 EPVPT 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 importance of hyperhomocysteinemia but also the concurrence of multiple risk factors in portal vein thrombosis.1 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 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 metabolite 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. As mentioned by Spanier and Frederiks, this 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, the association of increased 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 methylenetetrahydrofolate reductase gene avoids the problem of acquired hyperhomocysteinemia, this genetic defect itself does not appear to be a significant independent risk factor for atherothrombotic disease. 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.

Ongoing prospective controlled trials are investigating the potential beneficial effect of homocysteine lowering treatment on cardiovascular morbidity and mortality in subjects with hyperhomocysteinemia. Before advocating widespread screening for hyperhomocysteinemia 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 hepatoxicity when given rifampicin to treat their cholestatic pruritus (Gut 2002; 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 sequestran.

We would like to call attention to a recent abstract indicating that colesevelam, a new bile acid sequestran, appears to be more potent than cholestyramine and does not induce constipation.

This view that bile acid sequestrans causes pruritus is a very old one. Varco in 1947 noted that biliary drainage reduced pruritus in patients with extrahepatic biliary obstruction and that when bile was fed to patients, pruritus returned. Huet and colleagues reported that biliary drainage improved cholestatic pruritus in patients with inhepatic cholestasis. Administration of cholestyramine, an anion exchange resin with high affinity for bile acids, improved pruritus as did passage of plasma over charcoal or anion exchange resins. More recently, extracorporal bile acid removal, a procedure that removes bile acids, has been shown to diminish cholestatic pruritus. All in 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 ileal 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. 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 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 colesevelam, a new bile acid sequestrant, could have been removed at the same time so that cause and effect relationships were uncertain.

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, plasma bile acids fluctuates diurnally and the correlation between plasma bile acid levels and pruritus does not exclude a causal role for bile acids. Secondly, bile acids might cause and effect relationships were uncertain.

Secondly, bile acids might cause or partially mediate the release of substances that act on the skin, such as bile acids causes pruritus. This genetic defect by itself does not appear to be a significant independent risk factor for atherothrombotic disease. 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.

Ongoing prospective controlled trials are investigating the potential beneficial effect of homocysteine lowering treatment on cardiovascular morbidity and mortality in subjects with hyperhomocysteinemia. Before advocating widespread screening for hyperhomocysteinemia in patients with portal vein thrombosis, it would be preferable to have a better understanding of the clinical efficacy of these therapeutic interventions.
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 GelEx Pharmaceuticals (now Genzyme General) with a much superior binding affinity for bile acids. Colesevalem is a hydrogel that was developed as therapy for hypercholesterolaemia. Berg, in a recent abstract, reported that in eight patients with cholesterlamin pruritus who had not responded to cholestyramine, colesevalem was effective in five. Colesevalem has an additional advantage over cholestyramine in that colesevalem 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 of bile acids (now Genzyme General) with a much greater metabolic effect on bile acids. Colesevalem is a hydrogel that was developed as therapy for hypercholesterolaemia. Berg, in a recent abstract, reported that in eight patients with cholesterlamin pruritus who had not responded to cholestyramine, colesevalem was effective in five. Colesevalem has an additional advantage over cholestyramine in that colesevalem does not have gastrointestinal side effects.

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 of the 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 in total). We raised many dropouts because of the long term safety and concern over their safety? If the latter, then such a conclusion. As stated in the article, the oats products were free of contamination. If oats 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 nutritionist. As stated in the article, patients had free choice regarding the amount of oats they wished to consume and which they felt convenient. In this respect the study also depends 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 nutritionist. As stated in the article, patients had free choice regarding the amount of oats they wished to consume and which they felt convenient. In this respect the study also depends 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 nutritionist.
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 submission deadline) is due by 31 December 2002. 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 for coronary heart disease and diet, brain nutrition, gut nutrition, and a diet and lifestyle intervention session. Further information: Nutrition and Health Conference, 16 Browndale Court, Lythetlon Road. London N2 0EA; tel: +44 (0)208 455 6570; fax: +44 (0)20 455 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@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, Imەedex, 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. This year, was responsible for creating hepatology 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)20 7433 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: rhodesjin@liverpool.ac.uk
Aetiology of extrahepatic portal vein thrombosis

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