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 such as 200 mmol/day sodium for one week or when challenged with an intravenous saline load.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 systems3 which are responsible for the sublate sodium retention in these patients. Preascites is further characterised by increased dopaminergic activity,4 a possible consequence of the expanded intravascular volume, and elevated plasma nitric oxide levels,5 which in part contributes to the glomerular hyperfiltration observed in these patients.6 Finally, preascitic patients also have increased muscle sympathetic nervous activity7 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 hyperhomocysteinaemia as a relatively new, not yet mentioned, risk factor.8 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

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References


Terlipressin and arterial blood volume after paracentesis for tense ascites in cirrhosis

Moreau et al described the use of terlipressin, a vasopressin analogue, in ameliorating the reduction in effective arterial blood volume which can occur after paracentesis for tense ascites in cirrhosis (Gut 2002;50:90–4).

The article states that the first 1 mg intravenous bolus dose of terlipressin was given at the onset of paracentesis. Previous work has shown that infusion of vasopressin in a haemodynamically stable circulation can lead to reduced cardiac performance and coronary blood flow. Moreover, a sustained pressor response can occur in cirrhotic patients, with reduction in heart rate, cardiac output, hepatic blood flow, and pressor effects also on the pulmonary circulation.1

Although the authors state no episodes of arterial hypertension occurred in the terlipressin group and that there were no observed changes between pre- and post-treatment electrocardiograms (ECGs), it is not clear whether invasive continuous arterial pressure monitoring was employed in this study or whether continuous ECG readings were taken. Without this level of observation it is difficult to exclude the occurrence of transient asymptomatic episodes of cardiac ischaemia.

Exclusion of patients with a history of cardiac disease, cardiac failure, renal disease, and diabetes mellitus may render the conclusions of this pilot study, and those of any subsequent randomised controlled trials with the same exclusion criteria, difficult to interpret and apply. One may argue that it is these subgroups of patients with comorbid factors who are most likely to suffer the deleterious consequences of a reduction in effective arterial blood volume of any duration or magnitude.

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References

using the progesterone norethisterone (Prinhol 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 thrombophilies 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) gene: C677T mutation. Mild hyperhomocysteinaemia (fasting/six hour post methionine load values 18.91/19.91 μmol/l) was also detected. Plasma vitamin B_{6}, B_{12}, 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 venous thrombosis. Of the time of the study 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 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 EPVT as vitamin B_{6} 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 hyperhomocysteinaemia in a patient with portal vein thrombosis. Their case not only illustrates the potential importance of hyperhomocysteinaemia but also the concurrence of multiple risk factors in portal vein thrombosis. Two inherited thrombotic risk factors (methyleneetrahydrofolate 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 pathophysiologic 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 recognized as an established thrombogenic risk factor at the time of diagnosis. Furthermore, the risk of vitamin B_{6} deficiency 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 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 B_{12}) 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 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, colesevalem, was synthesised by GelTex Pharmaceuticals (now Genzyme General) with a much superior binding affinity for bile acids. Colesevalem is a hydrogel that was developed as therapy for hypercholesterolemia. Berg, in a recent abstract, reported that in eight patients with cholestatic pruritus who had not responded to cholestyramine, colesevalem was effective in five.¹ 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 intestinal side effects.

As stated in the article, patients had free choice regarding the amount of oats they wished to consume and which they felt were safe. In our original study (Gut 2002;50:332–5) the number of study patients in the oats group in remission in the original study (Gut 2002;50:332–5) should be 26 and not 12. The initial study 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 variably consenting volunteers, thus introducing selection bias to compliance. The number of dropouts, especially in the control group, was surprisingly high (41 out of 60). There was no indication of any deterioration 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 way in the control group or in the group where the control group was in fact including oats in their diet, 45 and 47 patients respectively—so only one study group was in fact including oats in their diet. The group who were in fact including oats in their diet were part of their gluten free products were substituted by oats.

After 12 months, patients used oat products from major Finnish manufacturers. They had 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 small intestinal biopsies carried out blindly by an experienced pathologist.

The values for the various antibody levels were statistically analysed comparing them at the end of the original study and at the five year time point. There were no statistically significant differences between time points or between the oats and control 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.
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 for coronary heart disease and diet, brain nutrition, gut nutrition, and diet and lifestyle intervention session. Further information: Nutrition and Health Conference, 16 Brownlow Court, Lyttleton Road, London N2 0EA; tel: +44 (0)203 455 6570; fax: +44 (0)203 455 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: oinfo@hkde.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 89 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 meeting will be held on 10–11 February 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