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”.

R H Wachsberg
Professor of Radiology, UMDNJ-University Hospital, 150 Bergen Street, Room C-320, Newark, NJ, USA, wachslbh@umdnj.edu

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 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”.

G Singh Ranger
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References


Aetiology of extrapathetic 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 extrapathetic 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.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 supplements. One day prior to admission she was taken. Without this level of observation pressure monitoring was employed in 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.

G Singh Ranger
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St George’s Hospital Medical School, Blackshaw Road, London SW17 OQT, UK, gisinghranger@yahoo.co.uk

References

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 which 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 mutation. Mild hyperhomocysteinaemia (fasting/six-hour post methionine load values 18.91 mmol/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 portal vein thrombosis. 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 B₆ and folate supplementation is a cheap and safe therapy in preventing deleterious vascular complications.

B W M Spanier, J Frederiks
Department of Internal Medicine, Spaarne Ziekenhuis Heemstede, Händellaan 2, 2102 CW Heemstede, the Netherlands

Correspondence to: B W M Spanier; b.w.m.spanier@freeler.nl

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 (methylenetetrahydrofolate and prothrombin gene G20210A mutation) predisposed the patient to a thrombotic event which became clinically manifest after the recent start of progesterone.

There 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. We mentioned Spanier and Frederiks in this letter 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 we have discovered some concordant morbidity 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 risk that the treatment may itself 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 concentration. 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 advancing 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.

H L A Janssen
Department of Gastroenterology and Hepatology, University Hospital Rotterdam, Dr Molewaterplein 40, 3015 GA Rotterdam, the Netherlands; devlam@mdm.ax.nl

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 2000;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 sequestrant. Use of this agent is frequently unsuccessful because of gastrointestinal side effects, especially constipation. I am writing to summarise new evidence that retention of endogenous bile acids causes cholestasis, and to draw attention to a recent abstract indicating that colesvemal, a new bile acid sequestrant, appears to be more potent than cholestyramine and does not induce constipation.

The view that bile acid retention 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, their pruritus returned. Huet and colleagues reported that biliary drainage improved cholestatic pruritus in patients with intrapathic 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 biliary cholestasis 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 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 ideal loop bypass was effective in relieving 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 either 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. Dabestani and colleagues noted 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, 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 K₅, for the ileal transport system is in the micromolar range, and at this concentration
 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 Pharmatech (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. 6 If this could be shown 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 cytochrome P450, a microsomal enzyme, whose synthesis is induced by the interaction of rifampicin and the nuclear receptor PXR. PXR activation might also induce bile acid synthesis. If the use of rifampicin is hazardous in cholestatic disease, as suggested by Prince et al., then treatment of cholestatic pruritus should involve a bile acid sequestrant 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.

A F Hofmann
Division of Gastroenterology, Department of Medicine, University of California, San Diego 92093-0813, USA; hofmannaf@cs.com

Conflict of interest Professor Hofmann has served as a paid consultant of GelTex Pharmaceuticals and has received stock options for the purchase of shares in that company.

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 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 in total). There were so many 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 time period between the two groups—months and 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 patient was 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 oats 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.

The safety of oats in coeliac disease is extremely important. Thus far this study has 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.

R Dor, DJ Shananah
Academic Unit of Medical and Surgical Gastroenterology, Homerton University Hospital, London E9 6SR, UK
Correspondence to: R Dor; riaz.dor@homerton.nhs.uk

Reference

Authors’ reply

Dor and Shananah point out the inconsistency in the number of study patients in the flow chart in figure 1 of our study on oats and gluten free diets (Gut 2002;50:332–5). They argue that there were no dropouts in the oats group and no significant error. Indeed, there is an error. The number of patients in the oats group in remission in the original study (Gut 1995;36:332–5) should have been 26 and not 12. The figures given in the text are however correct.

Dor and Shananah also emphasise the total number of dropouts (41) which covers both the original study of 6–12 months and the follow up of 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 those consuming oats (22). There was no evidence that the oats products were unpalatable. 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 biopsies. As expressed in the text, many patients also felt uncertain about long term safety. Hence, the low numbers in the control group were not due to fear, only the result of a natural process.

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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.

R Julkunen
Gastroenterological Unit, Department of Medicine, Kuopio University Hospital, Kuopio, Finland

M Uusitupa
Department of Clinical Nutrition, University of Kuopio, PO Box 1627 70211, Kuopio, Finland

Correspondence to: M Uusitupa; Matti.Uusitupa@uku.fi

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), simple application, rapid (60 day) peer review, and funding. Criteria for funding include 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: Mariana 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 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 1–3 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 Centenize 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 N J 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 5254; 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, UK. 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, Daubly Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesj@liverpool.ac.uk