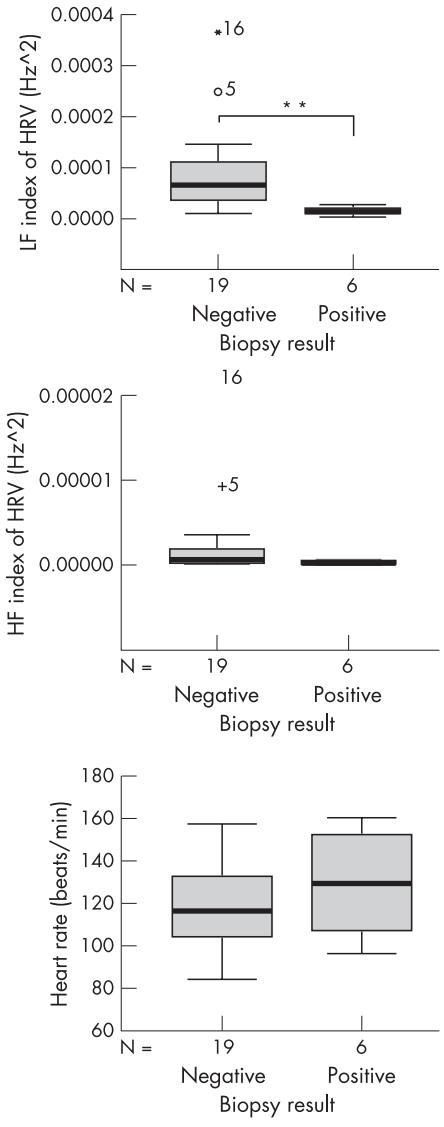

Figure 2 Box plots (median, upper and lower quartiles, and range) showing heart rate variability (HRV) measures, demonstrating a significant difference (**$p<0.005$) between biopsy positive and biopsy negative animals (Mann–Whitney test following a Kolmogorov–Smirnov test with Lilliefors significance correction to test for a normal distribution). There is no significant difference in the heart rates of the animals or in the high frequency range of HRV. Within the negative biopsy group, there was no difference in either low frequency or high frequency between the orally challenged and non-infected animals.

dysfunction caused by the presence of PrP^d in brain stem regions before clinical signs become noticeable.

PrP^d has been detected in vCJD rectal samples and implications for potential iatrogenic infection to humans of susceptible genotypes have been drawn.[1 2] Large scale studies of sheep scrapie show that PrP^d aggregates are consistently present in the recto-anal-mucosa-associated lymphoid tissue (RAMALT) of preclinically and clinically infected sheep.[7 8] This pilot study investigated the possibility that HRV might also recognise TSE infection in clinically normal sheep, positive for PrP^d in RAMALT biopsies.

Table 1 Summary of the genotypes of the sheep involved in the study

	Negative biopsy	Positive biopsy
Unexposed	2 ARQ/ARQ 1 VRQ/VRQ	–
Oral exposure	4 ARQ/ARQ	3 ARQ/ARQ 3 VRQ/VRQ
Natural exposure	9 ARR/ARR 2 ARQ/ARR 1 ARQ/ARQ	–

ARR/ARR and ARQ/ARR are resistant genotypes.

We recorded HRV data from 25 sheep. Six were clinically normal but PrP^d positive in RAMALT biopsies, and 19 were clinically normal and PrP^d negative in RAMALT biopsies. Among the latter, three were unchallenged controls, 11 were naturally exposed to scrapie infection and of resistant PrP genotypes, one was naturally exposed to scrapie and of susceptible genotype, and four were orally dosed and of susceptible genotypes. Experimentally infected sheep had been dosed with 5 g of a 10% homogenate of a pool from scrapie affected sheep brains.

ECG samples (300 s) were collected and digitised using a commercially available monitor (VariaCardio). ECG R wave timings were obtained to determine variability in the R–R intervals, and an instantaneous tachygram was constructed (fig 1) from which power spectra were calculated.

Power spectral analysis in the 0.032 to 0.138 Hz band (LF), but not the 0.15 to 0.5 Hz band (HF) showed significant differences (LF, $p<0.005$) between RAMALT biopsy negative and biopsy positive sheep (fig 2). As all positive sheep were asymptomatic, HRV assessment may be a useful preclinical test for TSE infection. This HRV index on its own, used once, may not distinguish between individual rectal biopsy positive animals and controls, as ranges overlapped. However, the negative and positive biopsy groups contained animals of different provenance—the negative biopsy group contained sheep of resistant genotypes, unexposed sheep, and sheep of uncertain infection status; the positive group contained infected sheep at approximately 40–90% of the incubation period. Owing to the small number of sheep investigated here, further large scale studies are needed to refine the methods and aid the interpretation of the results; however, being a live non-invasive screen for TSE infection it has the advantage that repeated measures over time may be taken to strengthen confidence in the interpretation.

We have previously demonstrated a similar reduction in HRV in BSE infected cattle[9] and in humans incubating vCJD[10] compared with controls. We herewith show that changes in HRV may be a common and early feature of TSE infections. Improved preclinical testing for TSEs using specific signature changes in HRV with respect to time could help minimise the risk of iatrogenic infection from endoscopy and other invasive procedures, and also provide an objective measure of the pathogenesis of the disease.

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Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver injury in many countries around the world.[1] NAFLD covers a wide spectrum, ranging from simple steatosis—which is generally non-progressive—to non-alcoholic steatohepatitis (NASH). There are no established non-invasive methods of evaluation for patients with NASH, and until recently liver biopsy was the only method for evaluating liver fibrosis. Transient elastography is a new technique that allows rapid, non-invasive measurement of mean tissue stiffness, which has been shown to be useful for accurate estimation of hepatic fibrosis in patients with chronic hepatitis C.[2]

We carried out a study to determine the value of liver stiffness measurement with the new medical device called the Fibroscan (EchoSens, Paris, France), based on ultrasound transient elastography, in patients with NAFLD. We carried out liver stiffness measurements in 67 NAFLD patients (mean (SD) age, 50.4 (3.3) years) in whom the diagnosis had

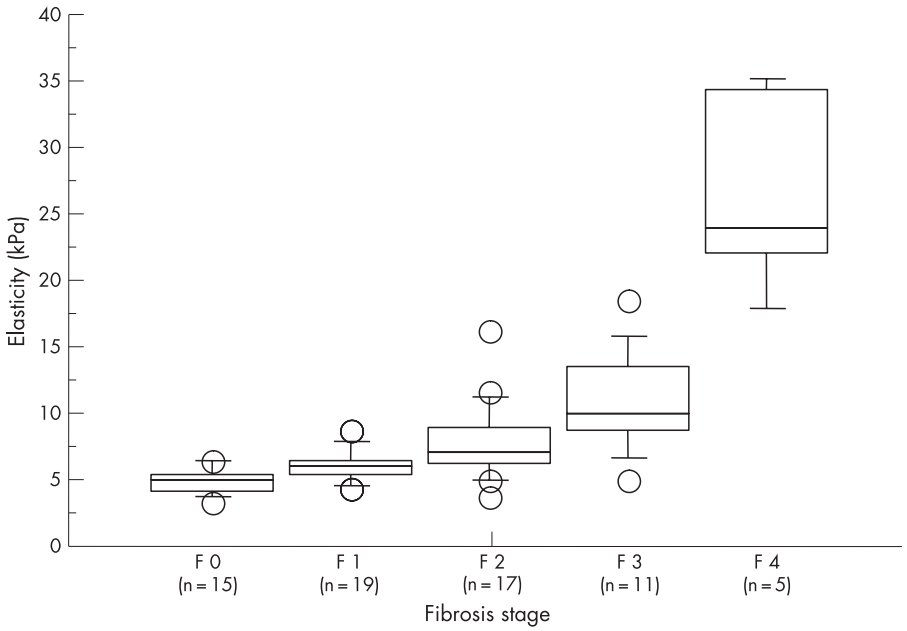

Figure 1 Box plots showing the interquartile range (box), median (thick line), range (thin lines), and outliers (circles) of liver stiffness measurements. A steady stepwise increase in elasticity was observed as the severity of hepatic fibrosis.

Table 1 Value of liver stiffness measurements in non-alcoholic fatty liver disease for estimating the stage of liver fibrosis

	Cut off value	Se (%)	Sp (%)	PPV (%)	NPV (%)
F>1 (F 0 *vs* F 1–4)	5.60 (kPa)	82.7	81.3	93.5	59.1
F>2 (F 0, 1 *vs* F 2–4)	6.65 (kPa)	81.8	91.2	90.0	83.8
F>3 (F 0–2 *vs* F 3, 4)	8.00 (kPa)	87.5	84.3	63.6	95.6
F>4 (F 0–3 *vs* F 4)	17.0 (kPa)	100	98.4	83.3	100

NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

been confirmed by liver biopsy and the severity of fibrosis had been scored according to Brunt.[3] Box plots were prepared to show the elasticity measurements according to the stage of histological fibrosis (fig 1). The median liver stiffness values (with 95% confidence intervals) were F 0, 4.907 (4.417 to 5.396) kPa; F 1, 6.142 (5.582 to 6.702) kPa; F2, 7.894 (6.384 to 9.404) kPa; F3, 11.027 (8.555 to 13.500) kPa; F4, 26.960 (17.705 to 36.215) kPa. The results of the analysis revealed stepwise increases in liver stiffness with increasing histological severity of hepatic fibrosis ($p<0.0001$ by Kruskal–Wallis test). The areas under the receiver operating characteristic curves (AUROC)—which estimate the diagnostic performance of the elasticity measurements for hepatic fibrosis stage equal to or greater than F 1, F 2, F 3, and F 4—were 0.881, 0.876, 0.914, and 0.997, respectively. Table 1 shows the optimal liver stiffness cut off values for NAFLD patients. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

The results of our study showed a significant positive correlation between liver stiffness and the severity of liver fibrosis in patients with NAFLD. Rapid, non-invasive estimation of the stage of fibrosis in NAFLD patients, especially NASH patients, is of major clinical interest because such patients have been shown to be at a high risk of developing complications such as portal hypertension or hepatocellular carcinoma, and therefore require close follow up. On the other hand, liver tissue containing fat deposition is presumably softer than healthy liver parenchyma, and sound velocity has been reported to decrease as fatty liver progressed in an animal experiment. However, the results of the present study also confirmed that the correlation between liver stiffness and the severity of fibrosis is unaffected by the grade of activity or degree of steatosis.[4]

The results show that liver stiffness measurements are a useful means of estimating the severity of hepatic fibrosis in NAFLD patients. This is the first study to demonstrate a consistent and major increase in liver stiffness in NASH patients, as confirmed by the results of liver biopsy, which remains the gold standard for evaluation of the severity of liver fibrosis in such patients. Liver stiffness measurement is a non-invasive, clinically useful method for estimating the severity of liver fibrosis in NASH.

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BOOK REVIEWS

The Enterobacteria, 2nd Edition

Edited by J Michael Janda, Sharon L Abbott. Washington: ASM Press, 2006, £87 (hardback), pp 411. ISBN 978-1-55581-342-0

As a microbiologist, having collaborated with quite a few gastroenterologists and gastrointestinal surgeons on past and current research projects, I am convinced most, if not all, have a great interest in bacterial infection. They might not care to admit it, but gastroenterologists have a common interest in the microbes that both inhabit and clinically infect the gastrointestinal tract and, in my experience, leap at the chance of investigating shared mechanisms of microbial inflammation, bacterial attachment to gut tissue, mechanisms of diarrhoeal disease and the collective chaos that some bacteria inflict on the gastrointestinal mucosa.

With this in mind, I was happy to receive the 2nd edition of *The Enterobacteria* for review (having previously purchased the 1st edition). As prefaced by the authors, this book is aimed as ''a reference source for microbiologists, physicians, infectious disease specialists, pathologists, epidemiologists, infection control practitioners and scientists (research, presumably) who need in-depth information on these bacteria''.

Why would the gastroenterologist be interested in such a publication, surely information they could already get in some of the larger gastroenterology or infectious disease texts? The beauty of this book is in its excellent reviews of all the usual suspects (*Salmonella*, *Shigella*, *E coli*, etc), but also in some of the more obscure and new bacterial genera currently classified within the Enterobacteriaceae. This volume is exceedingly useful for getting to grips with these organisms and, although the niceties of molecular classification and taxonomy may not interest the practising clinician, the clinical information and epidemiology of, for example, *Edwardsiella tarda* (an organism that is probably associated with more disease than is currently recognised) in this volume is timely, concise and useful. As a microbiologist, the advantage of this book is that all the genera are contained within one volume, with both clinical and microbiological information together. Should you buy it? If you have an overwhelming fascination with these organisms—definitely; if not, order one for the library.