



# *International Publications and Communications*

Revised April 1<sup>st</sup>, 2014

**CONTENT**

**PUBLICATIONS**

**WORLD JOURNAL OF GASTROENTEROLOGY, 2014 – IN PRESS**  
 Controlled Attenuation Parameter for the non-invasive assessment of hepatic steatosis in Chinese patients ..... 5

**JOURNAL OF HEPATOLOGY, 2014- IN PRESS**  
 Getting closer to a point-of-care diagnostic assessment in patients with chronic liver disease: Controlled Attenuation Parameter for steatosis..... 5

**JOURNAL OF GASTROENTEROLOGY HEPATOLOGY, 2014- IN PRESS**  
 Controlled Attenuation Parameter for the detection and quantification of hepatic steatosis in non-alcoholic fatty liver disease..... 5

**JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY, 2014- IN PRESS**  
 Controlled Attenuation Parameter for the detection of steatosis severity in chronic liver disease: A meta-analysis of diagnostic accuracy ..... 6

**JOURNAL OF HEPATOLOGY, 2013- IN PRESS**  
 Controlled Attenuation Parameter (CAP) for the diagnosis of steatosis: a prospective study of 5,323 examinations ..... 6

**HEPATOLOGY RESEARCH, 2013- IN PRESS**  
 Utility of Controlled Attenuation Parameter measurement for assessing liver steatosis in Japanese patients with chronic liver diseases ..... 6

**LIVER INTERNATIONAL, 2013- IN PRESS**  
 How good is Controlled Attenuation Parameter and fatty liver index for assessing liver steatosis in general population: correlation with ultrasound..... 7

**HEPATOLOGY RESEARCH, 2013- IN PRESS**  
 Editorial: Utility of Controlled Attenuation Parameter (CAP) measurement for assessing liver steatosis in Japanese patients with chronic liver diseases..... 7

**PLOS ONE INTERNATIONAL, 2014 MARCH; 9(3):E91987**  
 Non-Invasive Assessment of Hepatic Steatosis in Patients with NAFLD Using Controlled Attenuation Parameter and 1H-MR Spectroscopy..... 7

**LIVER INTERNATIONAL, 2014 JAN;34(1):102-9**  
 Controlled Attenuation Parameter (CAP) for detection of hepatic steatosis in patients with chronic liver diseases: a prospective study of a native Korean population ..... 8

**EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY, 2013- NOV;25(11):1330-1334**  
 Noninvasive detection of hepatic steatosis in patients without ultrasonographic evidence of fatty liver using the Controlled Attenuation Parameter evaluated with transient elastography ..... 8

**KIDNEY BLOOD PRESS RES 2013;37:305-310**  
 Chronic Kidney Disease and Nonalcoholic Fatty Liver Disease Proven by Transient Elastography ..... 9

**JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY, 2013- JUL;28(7):1194-1201**  
 Controlled Attenuation Parameter for Non-invasive Assessment of Hepatic Steatosis: Does aetiology affect performance..... 9

**EUROPEAN JOURNAL OF GASTROENTEROLOGY & HEPATOLOGY, 2013 AUG;25(8):905-11**  
 Interobserver concordance in Controlled Attenuation Parameter measurement, a novel tool for the assessment of hepatic steatosis on the basis of transient elastography..... 9

**LIVER INTERNATIONAL, 2012 JUL;32(6):911-8**  
 Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography... 10

**LIVER INTERNATIONAL, 2012 JUL;32(6):902-10**  
 Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography ..... 10

**JOURNAL OF VIRAL HEPATITIS, 2012 APR;19(4):244-53**  
 Novel Controlled Attenuation Parameter (CAP) for noninvasive assessment of steatosis using Fibroscan®: validation in chronic hepatitis C ..... 11

**CLINICS & RESEARCH IN HEPATOLOGY & GASTROENTEROLOGY, 2012 FEB;36(1):13-20**  
 The controlled attenuation parameter (CAP): A novel tool for the non-invasive evaluation of steatosis using Fibroscan ..... 11

**ULTRASOUND IN MEDICINE & BIOLOGY, 2010 NOV;36(11):1825-35**  
 Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis - Preliminary study and validation in a cohort of patients with chronic liver disease from various causes..... 11

**COMMUNICATIONS**

**POSTER EASL 2014 (APR 9-13)**  
 Liver steatosis assessment with CAP at 3.5 Mhz using FibroScan M and XL Probe ..... 12

**POSTER EASL 2014 (APR 9-13)**  
 Predictors of hepatic steatosis in a prospective study of European untreated hepatitis b surface antigen (HBSAG) carriers: evaluation by Controlled Attenuation Parameter (CAP)..... 12

**POSTER EASL 2014 (APR 9-13)**  
 Patients with T2DM accompanying severe degree of NAFLD assessed by Controlled Attenuation Parameter using FibroScan ..... 12

**POSTER EASL 2014 (APR 9-13)**  
 The Common PNPLA3 Variant is associated with hepatic steatosis quantified by Controlled Attenuation Parameter and determines the fate of patients with chronic liver diseases ..... 13

**POSTER EASL 2014 (APR 9-13)**  
 Non-invasive characterization of post-transplant fatty liver disease reveals high prevalence of graft injury in association with metabolic syndrome, recipient PNPLA3 genotype and alcoholic liver cirrhosis..... 13

<b>POSTER AASLD 2013 (NOV 1<sup>ST</sup>-5)</b>	
Liver steatosis, presumed by SteatoTest or Controlled Attenuation Parameter (CAP), is associated to a risk of false-positive liver stiffness measurement by transient elastography in type-2 diabetic patients.....	14
<b>POSTER AASLD 2013 (NOV 1<sup>ST</sup>-5)</b>	
Comparison between results of hepatic transient elastography (FibroScan®) and Controlled Attenuation Parameter (cap™) versus liver biopsy in NAFLD Patients.....	14
<b>POSTER APASL 2013 (JUNE 6-10)</b>	
Influencing Factors and Reproducibility of Controlled Attenuation Parameters (CAP) in the Evaluation of Fatty Liver Disease Using FibroScan .....	15
<b>POSTER APASL 2013 (JUNE 6-10)</b>	
A Promising Clinical Utility of the Controlled Attenuation Parameter (CAP) for Noninvasive Assessment of Steatosis Using Fibroscan .....	15
<b>POSTER APASL 2013 (JUNE 6-10)</b>	
Noninvasive Detection of Hepatic Steatosis in Subjects without Ultrasonographic Evidence of Fatty Liver Using the Controlled Attenuation Parameter (CAP) .....	15
<b>POSTER EASL 2013 (APRIL 24-28)</b>	
Interobserver concordance in Controlled Attenuation Parameter (CAP) measurement, a novel tool for the assessment of hepatic steatosis based on transient elastography.....	16
<b>POSTER EASL 2013 (APRIL 24-28)</b>	
Non-invasive measurement of liver steatosis by Controlled Attenuation Parameter (CAP) using FibroScan® in patients with Nonalcoholic Fatty Liver Disease (NAFLD) .....	16
<b>POSTER CROI 2013 (MARCH 3-6) 17</b>	
Inter-observer concordance in Controlled Attenuation Parameter Measurement, a novel tool for the assessment of hepatic steatosis.....	17
<b>POSTER CROI 2013 (MARCH 3-6)</b>	
Prevalence and Factors Associated with Liver Steatosis Measured by Transient Elastography with Controlled Attenuation Parameter in HIV Infection .....	17
<b>POSTER AASLD 2012 (NOVEMBER 9-13)</b>	
Controlled Attenuation Parameter (CAP) for the detection of hepatic steatosis in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) .....	18
<b>POSTER EASL 2012 (APRIL 18-22)</b>	
The performance of controlled attenuation parameter (CAP) for the non-invasive evaluation of steatosis using FibroScan®. Preliminary results.....	18
<b>ORAL PRESENTATION AIUM 2012 (MARCH 29-APR. 1<sup>ST</sup>)</b>	
Controlled Attenuation Parameter (CAP): a novel FibroScan®-based tool to assess liver steatosis .....	19
<b>POSTER APASL 2012 (FEB. 16-19)</b>	
Hepatology perisinusoidal fibrosis is associated with transient elastography (TE) and Controlled Attenuation Parameter (CAP) values measured by FibroScan® .....	19
<b>POSTER AASLD 2011 (NOV. 4-8)</b>	
Steatosis assessment by CAP™ in patients with alcoholic and non-alcoholic fatty liver disease.....	20
<b>ORAL PRESENTATION EASL 2011 (MARCH 30-APRIL 3<sup>RD</sup>)</b>	
Non Invasive diagnosis of steatosis using CAP by FibroScan®. A prospective study .....	20
<b>POSTER APASL 2011 (FEB. 17-20)</b>	
Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis in chronic hepatitis B .....	21
<b>ORAL PRESENTATION APASL 2011 (FEB. 17-20)</b>	
Non invasive diagnosis of steatosis using CAP by FibroScan® .....	21
<b>ORAL PRESENTATION AASLD 2010 (OCT. 29-NOV. 2<sup>ND</sup>)</b>	
Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis in chronic hepatitis B. ....	22
<b>POSTER AASLD 2010 (OCT. 29-NOV. 2<sup>ND</sup>)</b>	
CAP: a VCTE™-guided tool for hepatic steatosis detection – Preliminary results of a multicenter study in overweight and obese patients with chronic liver disease .....	22
<b>ORAL PRESENTATION I.E.E.E. 2010 (OCT. 1-14)</b>	
Controlled Attenuation Parameter (CAP): a novel VCTE™-guided tool to detect and quantify steatosis. principle and validation on field II simulations, tissue mimicking phantoms and clinically on patients with chronic liver disease.....	23
<b>ORAL PRESENTATION ICO 2010 (JULY 11-15)</b>	
A novel non-invasive FibroScan®-based tool for the detection of hepatic steatosis in overweight and obese patients .....	23
<b>POSTER EASL 2010 (APRIL 14-18)</b>	
Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis. preliminary study in patient with alcoholoc and nonalcoholic fatty liver disease.....	24
<b>ORAL PRESENTATION EASL 2010 (APRIL 14-18)</b>	
Validation of Controlled Attenuation Parameter (CAP) as a non-invasive marker of steatosis in 228 patients with chronic liver disease from various causes.....	24
<b>ORAL PRESENTATION APASL 2010 (MARCH 25-28)</b>	
Controlled Attenuation Parameter for the detection and quantification of steatosis -Preliminary study in an alcoholic and non-alcoholic steato-hepatitis cohort.....	25
<b>POSTER AASLD 2009 (OCT. 30-NOV. 3<sup>RD</sup>)</b>	
Novel ultrasonic FibroScan®-based steatosis index for hepatic steatosis quantification in 618 HCV patients .....	25
<b>POSTER EASL-NASH 2009 (SEPT. 23<sup>RD</sup>-26)</b>	
Novel ultrasonic steatosis index for steatosis quantification - Validation in a large cohort of HCV patients - .....	26
<b>PROCEEDINGS ARTICLE - I.E.E.E. 2009 (SEPT. 19-23<sup>RD</sup>)</b>	
Novel Controlled Attenuation Parameter for the evaluation of fatty liver disease - A preliminary study on a large multi-etiology cohort .....	26

**POSTER I.E.E.E. 2009 (SEPT. 19-23<sup>RD</sup>)**

Development of an ultrasonic steatosis index for the  
evaluation of fatty liver disease .....29

## PUBLICATIONS

### World Journal of Gastroenterology, 2014 – *in press*

#### Controlled Attenuation Parameter for the non-invasive assessment of hepatic steatosis in Chinese patients

Feng Shen, Rui-Dan Zheng, Yu-Qiang Mi, Xiao-Ying Wang, Qin Pan, Guang-Yu Chen, Hai-Xia Cao, Ming-Li Chen, Liang Xu, Jian-Neng Chen, Yi Cao, Rui-Nan Zhang, Lei-Ming Xu, Jian-Gao Fan

1) Dpt of Gastroenterology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

2) Research & Therapy Center for Liver Diseases, The Affiliated Dongnan Hospital of Xiamen University, Zhangzhou, China

3) Tianjin Research Institute of Liver Diseases, Tianjin Hospital of Infectious Diseases, China

4) Dpt of Pathology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, China

5) Dpt of Ultrasound, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, China

**Aim:** To evaluate the performance of a novel non-invasive Controlled Attenuation Parameter (CAP) to assess liver steatosis.

**Methods:** This was a multi-center prospective cohort study. Consecutive patients (aged  $\geq 18$  years) who had undergone percutaneous liver biopsy and CAP measurement were recruited from three Chinese liver centers. Steatosis was categorized as S0:  $< 5\%$ ; S1: 5-33%; S2: 34-66%; S3:  $\geq 67\%$ , according to the nonalcoholic fatty liver disease (NAFLD) activity score. The FibroScan<sup>®</sup> 502 equipped with the M probe (Echosens, Paris, France) was used to capture both CAP and liver stiffness measurement (LSM) values simultaneously. Receiver operating characteristic curves were plotted, and the areas under the curves were calculated to determine the diagnostic efficacy. The accuracy of the CAP values at the optimal thresholds was defined by maximizing the sum of sensitivity and specificity (maximum Youden index).

**Results:** A total of 152 patients were recruited, including 52 (34.2%) patients with NAFLD and 100 (65.8%) with chronic hepatitis B (CHB) virus infection. After adjustment, the steatosis grade [odds ratio (OR) 37.12; 95% confidence intervals (CI) 21.63-52.60,  $P < 0.001$ ] and body mass index (BMI, OR 6.20; 95% CI 2.92-9.48,  $P < 0.001$ ) were found independently associated with CAP by multivariate linear regression analysis. CAP was not influenced by inflammation, fibrosis or aetiology. The median CAP values and interquartile range (IQR) among patients with S0, S1, S2 and S3 steatosis were 211 (181-240) dB/m, 270 (253-305) dB/m, 330 (302-360) dB/m, and 346 (313-363) dB/m, respectively. The cut-offs for the CAP values in all patients with steatosis  $\geq 5\%$ ,  $\geq 34\%$  and  $\geq 67\%$  were 253 dB/m, 285 dB/m and 310 dB/m, respectively. The areas under the curves were 0.92, 0.92 and 0.88 for steatosis  $\geq 5\%$ ,  $\geq 34\%$  and  $\geq 67\%$ . No significant differences were found in the CAP values between the NAFLD group and the CHB group in each steatosis grade.

**Conclusion:** CAP appears to be a promising tool for the non-invasive detection and quantification of hepatic steatosis, but is limited by BMI.

### Journal of Hepatology, 2014- *in press*

#### Getting closer to a point-of-care diagnostic assessment in patients with chronic liver disease: Controlled Attenuation Parameter for steatosis

Berzigotti A.

Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd); Barcelona Hepatic Hemodynamic Laboratory, Liver Unit. Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). University of Barcelona, Spain

No abstract is available

### Journal of Gastroenterology Hepatology, 2014- *in press*

#### Controlled Attenuation Parameter for the detection and quantification of hepatic steatosis in non-alcoholic fatty liver disease

Wah-Kheong Chan<sup>1</sup>, Nik Raihan Nik Mustapha<sup>2</sup>, Sanjiv Mahadeva<sup>1</sup>

1- Gastroenterology & Hepatology Unit, Gastrointestinal Endoscopy Unit, Dpt of Medicine, Faculty of Medicine, University of Malaya

2- Department of Pathology, Hospital Alor Setar

**Background:** Controlled Attenuation Parameter (CAP) has been suggested as a non-invasive method for detection and quantification of hepatic steatosis. We aim to study the diagnostic performance of CAP in non-alcoholic fatty liver disease (NAFLD) patients.

**Methods:** Transient elastography was performed in consecutive NAFLD patients undergoing liver biopsy and non-NAFLD controls. The accuracy of CAP for the detection and quantification of hepatic steatosis was assessed based on histological findings according to the Non-Alcoholic Steatohepatitis Clinical Research Network Scoring System.

**Results:** Data for 101 NAFLD patients (mean age  $50.3 \pm 11.3$  years old, 51.5% male) and 60 non-NAFLD controls were analyzed. CAP was associated with steatosis grade (OR=29.16,  $p < 0.001$ ), body mass index (BMI) (OR=4.34,  $p < 0.001$ ) and serum triglyceride (OR=13.59,  $p = 0.037$ ) on multivariate analysis. The median CAP for steatosis grades S0, S1, S2 and S3 were 184dB/m, 305dB/m, 320dB/m and 324dB/m, respectively. The AUROC for estimation of steatosis grades  $\geq S1$ , S2 and S3 were 0.97, 0.86 and 0.75, respectively. The optimal CAP cut-offs for estimation of steatosis grades  $\geq S1$ , S2 and S3 were 263dB/m, 281dB/m and 283dB/m, respectively. Among non-obese patients, the AUROC for estimation of steatosis grades  $\geq S1$  and S2 were 0.99 and 0.99, respectively. Among obese patients, the AUROC for estimation of steatosis grades  $\geq S1$ , S2 and S3 were 0.92, 0.64 and 0.58, respectively.

**Conclusions:** CAP is excellent for the detection of significant hepatic steatosis. However, its accuracy is impaired by an increased BMI and it is less accurate to distinguish between the different grades of hepatic steatosis.

**Journal of Gastroenterology & Hepatology, 2014-  
in press**

**Controlled Attenuation Parameter for the detection of steatosis severity in chronic liver disease: A meta-analysis of diagnostic accuracy**

Ke-Qing Shi<sup>1</sup>, Jun-Zhou Tang<sup>2</sup>, Xue-Lian Zhu<sup>3</sup>, Li Ying<sup>3</sup>, De-Wei Li<sup>4</sup>, Jian Gao<sup>5</sup>, Yu-Xiao Fang<sup>6</sup>, Gui-ling Li<sup>6</sup>, Yi-Jiang Song<sup>6</sup>, Zhu-Jun Deng<sup>6</sup>, Jian-Min Wu<sup>6</sup>, Kai-Fu Tang<sup>6</sup>

1. Dpt of Infection & Liver Diseases, Institution of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, China

2. Center of Bone Metabolism and Repair, State Key Laboratory of Trauma, Burns, & Combined Injury, Trauma Center, Daping Hospital & Research Institute of Surgery of the Third Military Medical University, Chongqing, China

3. Dpt of Ultrasonography, the First Affiliated Hospital of Wenzhou Medical University, China

4. Dpt of Hepatobiliary Surgery, First Affiliated Hospital, Chongqing Medical University, China

5. Dpt of Gastroenterology, Second Affiliated Hospital, Chongqing Medical University, China

6. Institute of Genomic Medicine, Wenzhou Medical University, China

**Background & Aim:** Controlled Attenuation Parameter (CAP) is a novel ultrasound-based elastography method for detection of steatosis severity. This meta-analysis aimed to assess the performance of CAP.

**Methods:** PubMed, the Cochrane Library, and the ISI Web of Knowledge were searched to find studies, published in English, relating to accuracy evaluations of CAP for detecting stage 1 (S1), stage 2 (S2), or stage 3 (S3) hepatic steatosis which was diagnosed by liver biopsy. Sensitivities, specificities, and hierarchical summary receiver operating characteristic (HSROC) curves were used to examine CAP performance. The clinical utility of CAP was also evaluated.

**Results:** Nine studies, with 11 cohorts were analyzed. The summary sensitivities and specificities values were 0.78 (95% confidence interval [CI], 0.69-0.84) and 0.79 (95% CI, 0.68-0.86) for  $\geq S1$ , 0.85 (95% CI, 0.74-0.92) and 0.79 (95% CI, 0.71-0.85) for  $\geq S2$ , and 0.83 (95% CI, 0.76-0.89) and 0.79 (95% CI, 0.68-0.87) for  $\geq S3$ . The HSROCs were 0.85 (95% CI, 0.81-0.88) for  $\geq S1$ , 0.88 (95% CI, 0.85-0.91) for  $\geq S2$ , and 0.87 (95% CI, 0.84-0.90) for  $\geq S3$ . Following a "positive" measurement (over the threshold value) for  $\geq S1$ ,  $\geq S2$ , and  $\geq S3$ , the corresponding post-test probabilities for the presence of steatosis (pre-test probability was 50%) were 78%, 80% and 80%, respectively; if the values were below these thresholds ("negative" results), the post-test probabilities were 22%, 16%, and 17%, respectively.

**Conclusions:** CAP has good sensitivity and specificity for detecting hepatic steatosis; however, based on a meta-analysis, CAP was limited in their accuracy of steatosis, which precluded widespread use in clinical practice.

**Journal of Hepatology, 2013- in press**

**Controlled Attenuation Parameter (CAP) for the diagnosis of steatosis: a prospective study of 5,323 examinations**

de Lédinghen V<sup>1</sup>, Vergniol J<sup>2</sup>, Capdepon M<sup>3</sup>, Chermak F<sup>2</sup>, Hiriart JB<sup>2</sup>, Cassinotto C<sup>3</sup>, Merrouche W<sup>2</sup>, Foucher J<sup>2</sup>, le Bail B.<sup>4</sup>

**Background & aims:** Controlled Attenuation Parameter (CAP) evaluated with transient elastography

(FibroScan) is a recent method for non invasive assessment of steatosis. Its usefulness in clinical practice is unknown. We prospectively investigated the determinants of CAP failure and the relationships between CAP and clinical or biological parameters in a large cohort of consecutive patients.

**Methods:** All CAP examinations performed in adult patients with suspected chronic liver disease were included. CAP failure was defined as zero valid shot. The following factors were analyzed for their influence on CAP value and the relationships between CAP and clinico-biological parameters: age, gender, body mass index, waist circumference, hypertension, diabetes, metabolic syndrome, alcohol use, liver stiffness measurement, indication, and different biological parameters.

**Results:** CAP failure occurred in 7.7% of 5,323 examinations. By multivariate analysis, factors independently associated with CAP measurement failure were female gender, BMI, and metabolic syndrome. By multivariate analysis, factors significantly associated with elevated CAP were BMI [25-30] kg/m<sup>2</sup>, BMI > 30 kg/m<sup>2</sup>, metabolic syndrome, alcohol > 14 drink/week and liver stiffness > 6 kPa. CAP increased with the number of parameters of metabolic syndrome, BMI, waist circumference, the presence of diabetes or hypertension, and the cause of the disease. In the 440 patients with liver biopsy, for the diagnosis of steatosis > 10%, steatosis > 33%, and steatosis > 66%, AUROCs of CAP were 0.79 (95%CI 0.74-0.84, p<0.001), 0.84 (95%CI 0.80-0.88, p<0.001), 0.84 (95%CI 0.80-0.88, p<0.001), respectively

**Conclusion:** CAP provides an immediate assessment of steatosis simultaneously with liver stiffness measurement. The strong association of CAP with the metabolic syndrome and alcohol use could be of interest for the follow-up of NAFLD or alcoholic patients.

**Hepatology Research, 2013- in press**

**Utility of Controlled Attenuation Parameter measurement for assessing liver steatosis in Japanese patients with chronic liver diseases**

Masaki K, Takaki S, Hyogo H, Kobayashi T, Fukuhara T, Naeshiro N, Honda Y, Nakahara T, Ohno A, Miyaki D, Murakami E, Nagaoki Y, Kawaoka T, Tsuge M, Hiraga N, Hiramatsu A, Imamura M, Kawakami Y, Aikata H, Ochi H, Takahashi S, Arihiro K, Chayama K.

Dpt of Gastroenterology and Metabolism, Hiroshima University Hospital, Japan.

**Aim:** Steatosis is a common histological feature of chronic liver disease, especially alcoholic and non-alcoholic fatty liver disease, as well as chronic hepatitis C. A recent study showed that evaluating the controlled attenuation parameter (CAP) with transient elastography was an efficient way of non-invasively determining the severity of hepatic steatosis. The objective of this study was to prospectively evaluate the utility of CAP for diagnosing steatosis in patients with chronic liver disease.



**Methods:** One hundred and fifty-five consecutive patients with suspected chronic liver disease underwent steatosis diagnosis using CAP, blood sample analyses, computed tomography for assessing the liver/spleen ratio and liver biopsy. Steatosis was graded according to the percentage of fat-containing hepatocytes: S0, less than 5%; S1, 5-33%; S2, 34-66%; and S3: more than 66%.

**Results:** The CAP was significantly correlated with steatosis grade, and there were significant differences between the CAP value of the S0 patients and those of the patients with other grades of steatosis. S0 and S1-3 hepatic steatosis were considered to represent mild and significant steatosis, respectively. The CAP values of the patients with mild and significant steatosis were significantly different ( $P < 0.0001$ ). The area under the receiver-operator curve (AUROC) value of the CAP for diagnosing significant steatosis was 0.878 (95% confidence interval, 0.818-0.939), and the optimal CAP cut-off value for detecting significant steatosis was 232.5 db/m. In multivariate analysis, the CAP ( $P = 0.0002$ ) and the liver to spleen ratio ( $P = 0.004$ ) were found to be significantly associated with significant steatosis.

**Conclusion:** The CAP is a promising tool for rapidly and non-invasively diagnosing steatosis.

### Liver International, 2013- in press

#### How good is Controlled Attenuation Parameter and fatty liver index for assessing liver steatosis in general population: correlation with ultrasound

Sofia Carvalhana<sup>1</sup>, Jorge Leitão<sup>2</sup>, Ana C. Alves<sup>3</sup>, Mafalda Bourbon<sup>3</sup>, Helena Cortez-Pinto<sup>1,\*</sup>

1 Departamento de Gastroenterologia, Unidade de Nutric\_ao e Metabolismo, Hospital Santa Maria, CHLN, Faculdade de Medicina de Lisboa, Portugal

2 Unidade de Hepatologia, Servico de Medicina Interna, Centro Hospitalar e Universitario de Coimbra, Portugal

3 Unidade de I&D Grupo de Investigac\_ao Cardiovascular, Departamento de Promoc\_ao da Sa\_ude e Prevencao de Doenc\_as Transmiss\_veis, Center for BiodiversityFunctional & Integrative Genomics (BioFIG), Instituto Nacional de Sa\_ude Dr. Ricardo Jorge, Lisboa, Portugal

**Background & Aims:** Liver steatosis measurement by controlled attenuation parameter (CAP) is a non-invasive method for diagnosing steatosis, based on transient elastography. Its usefulness as screening procedure for hepatic steatosis in general population has not been previously evaluated. The aim of this study was to evaluate the diagnostic accuracy of CAP and fatty liver index (FLI) for detection and quantification of steatosis in general population.

**Methods:** Recruitment was done from a prospective epidemiological study of the general adult population. Steatosis was evaluated using CAP, FLI and ultrasound (US). Steatosis scored according to Hamaguchi's US scoring, from 0 (S0) to 6 (S6) points. Hepatic steatosis defined by score  $\geq 2$  (S $\geq 2$ ) and moderate/severe steatosis by score  $\geq 4$  (S $\geq 4$ ). Performance of CAP and FLI for diagnosing steatosis compared with US was assessed using areas under receiver operating characteristic curves (AUROC).

**Results:** From 219 consecutive individuals studied, 13 (5.9%) excluded because of failure/unreliable liver stiffness measurements. Steatosis prevalence: S $\geq 2$  38.4% and S $\geq 4$  12.1%. CAP significantly correlated with steatosis

( $\rho = 0.73$ ,  $P < 0.0001$ ), steatosis score ( $\rho = 0.76$ ;  $P < 0.0001$ ), FLI ( $\rho = 0.69$ ), waist circumference ( $\rho = 0.62$ ), body mass index ( $\rho = 0.55$ ), triglyceride ( $\rho = 0.49$ ), HOMA-IR ( $\rho = 0.26$ ), alcohol consumption ( $\rho = 0.24$ ) and cholesterol ( $\rho = 0.19$ ), not with liver stiffness measurements. Using CAP and FLI, AUROC's were 0.94 (95% CI 0.91-0.97,  $P < 0.001$ ) and 0.91 for S $\geq 2$ ; 0.95 (95% CI 0.90-0.99,  $P < 0.001$ ) and 0.93 for S $\geq 4$  respectively. Optimal cut-off value of CAP and FLI were 243 dB/m and 48 for S $\geq 2$ ; 303.5 dB/m and 62 for S $\geq 4$  respectively.

**Conclusion:** Controlled attenuation parameter and FLI seem promising tools for screening and steatosis quantification in the general population. Larger studies are needed for validation.

### Hepatology Research, 2013- in press

#### Editorial: Utility of Controlled Attenuation Parameter (CAP) measurement for assessing liver steatosis in Japanese patients with chronic liver diseases

Masato Yoneda, Division of Gastroenterology, Yokohama City University Hospital, 3-9 Fuku-ura, Kanazawa-ku, Yokohama, Japan

Along with the westernization of lifestyles, the prevalence of nonalcoholic fatty liver disease (NAFLD) has been increasing around the world in recent years. The estimated number of patients with NAFLD has reached 80-100 million in the U.S., 1-3) and the corresponding number of patients in Japan has been estimated at 10-20 million. The prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) is increasing and is becoming a major target disease not only in Western countries, but also in Japan. Not only NAFLD, but also hepatic steatosis is a common feature among patients with alcoholic liver disease (ALD) and those with hepatitis C viral infection. In patients with chronic hepatitis C, coexisting steatosis reportedly accelerates fibrosis progression and reduces the treatment response.4) Therefore, the ability to diagnose hepatic steatosis accurately is important for clinical evaluation.

### Plos One International, 2014 March; 9(3):e91987

#### Non-Invasive Assessment of Hepatic Steatosis in Patients with NAFLD Using Controlled Attenuation Parameter and 1H-MR Spectroscopy

Thomas Karlas<sup>1,2</sup>, David Petroff<sup>1,3</sup>, Nikita Garnov<sup>1,4</sup>, Stephan Böhm<sup>5</sup>, Hannelore Tenckhoff<sup>5</sup>, Christian Wittekind<sup>6</sup>, Manfred Wiese<sup>5</sup>, Ingolf Schiefke<sup>7</sup>, Nicolas Linder<sup>1,4</sup>, Alexander Schaudinn<sup>1,4</sup>, Harald Busse<sup>4</sup>, Thomas Kahn<sup>4</sup>, Joachim Mössner<sup>2</sup>, Thomas Berg<sup>5</sup>, Michael Tröltzsch<sup>2</sup>, Volker Keim<sup>2</sup>, Johannes Wiegand<sup>1,2,5\*</sup>

1) IFB AdiposityDiseases, Leipzig University Medical Center, Leipzig, Germany,

2) Dpt of Medicine, Neurology and Dermatology, Division of Gastroenterology & Rheumatology, University Hospital Leipzig, Germany,

3) Clinical Trial Center, University of Leipzig, Germany,

4) Dpt of Diagnostics & Interventional Radiology, University Hospital Leipzig, Germany,

5) Dpt of Medicine, Neurology and Dermatology, Division of Gastroenterology & Rheumatology, Section of Hepatology, University Hospital Leipzig, Germany,

6) Institute of Pathology, University Hospital Leipzig, Germany,

7) Clinic for Gastroenterology & Hepatology, Klinikum St. Georg, Leipzig, Germany

**Introduction:** Non-invasive assessment of steatosis and fibrosis is of growing relevance in non-alcoholic fatty liver disease (NAFLD). 1H-Magnetic resonance spectroscopy (1H-MRS) and the ultrasound-based controlled attenuation parameter (CAP) correlate with biopsy proven steatosis, but have not been correlated with each other so far. We therefore performed a head-to-head comparison between both methods.

**Methods:** Fifty patients with biopsy-proven NAFLD and 15 healthy volunteers were evaluated with 1H-MRS and transient elastography (TE) including CAP. Steatosis was defined according to the percentage of affected hepatocytes: S1 5-33%, S2 34-66%, S3 >67%.

**Results:** Steatosis grade in patients with NAFLD was S1 36%, S2 40% and S3 24%. CAP and 1H-MRS significantly correlated with histopathology and showed comparable accuracy for the detection of hepatic steatosis: areas under the receiver operating characteristics curves were 0.93 vs. 0.88 for steatosis S1 and 0.94 vs. 0.88 for S2, respectively. Bootstrapping analysis revealed a CAP cut-off of 300 dB/m for detection of S2-3 steatosis, while retaining the lower cut-off of 215 dB/m for the definition of healthy individuals. Direct comparison between CAP and 1H-MRS revealed only modest correlation (total cohort:  $r = 0.63$  [0.44, 0.76]; NAFLD cases:  $r = 0.56$  [0.32, 0.74]). For detection of F2-4 fibrosis TE had sensitivity and specificity of 100% and 98.1% at a cut-off value of 8.85 kPa.

**Conclusion:** Our data suggest a comparable diagnostic value of CAP and 1H-MRS for hepatic steatosis quantification. Combined with the simultaneous TE fibrosis assessment, CAP represents an efficient method for non-invasive characterization of NAFLD. Limited correlation between CAP and 1H-MRS may be explained by different technical aspects, anthropometry, and presence of advanced liver fibrosis.

**Liver International, 2014 Jan;34(1):102-9**

**Controlled Attenuation Parameter (CAP) for detection of hepatic steatosis in patients with chronic liver diseases: a prospective study of a native Korean population**

Young Eun Chon<sup>1,\*</sup>, Kyu Sik Jung<sup>1,\*</sup>, Seung Up Kim<sup>1,2,4</sup>, Jun Yong Park<sup>1,2,4</sup>, Young Nyun Park<sup>3</sup>, Do Young Kim<sup>1,2,4</sup>, Sang Hoon Ahn<sup>1,2,4,5</sup>, Chae Yoon Chon<sup>1,2,4</sup>, Hye Won Lee<sup>1</sup>, Yehyun Park<sup>1</sup> and Kwang-Hyub Han<sup>1,2,4,5</sup>

1 Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea  
2 Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea  
3 Department of Pathology, Yonsei University College of Medicine, Seoul, Korea  
4 Liver Cirrhosis Clinical Research Center, Yonsei University College of Medicine, Seoul, Korea  
5 Brain Korea 21 Project of Medical Science, Yonsei University College of Medicine, Seoul, Korea

**Background:** Controlled Attenuation Parameter (CAP) is a non-invasive method of measuring hepatic steatosis using a process based on transient elastography. We investigated the diagnostic accuracy of CAP in detecting hepatic steatosis in patients with chronic liver disease (CLD).

**Methods:** A total of 135 patients with CLD who underwent liver biopsy and CAP were consecutively

enrolled in this prospective study. The performance of CAP for detection of hepatic steatosis compared with liver biopsy was calculated using area under receiver operating characteristics curves (AUROC). Steatosis was categorized into S0 (<5%), S1 (5-33%), S2 (34-66%) and S3 (>66% of hepatocytes).

**Results:** Male gender predominated (n = 87, 64%) and the median age was 51 years. The aetiologies of CLD included non-alcoholic fatty liver disease (n = 56, 41.5%) and chronic viral hepatitis because of hepatitis B (n = 47, 34.8%) and C (n = 12, 8.9%). Steatosis repartition was: S0 31.1% (n = 42), S1 43.7% (n = 59), S2 18.5% (n = 25) and S3 6.7% (n = 9) respectively. In the multivariate analysis, steatosis grade and body mass index were independently associated with CAP (all P < 0.001), whereas fibrosis stage and activity grade were not. The AUROCs of CAP were 0.885 for  $\geq$ S1 (sensitivity 73.1%, specificity 95.2%), 0.894 for  $\geq$ S2 (sensitivity 82.4%, specificity 86.1%) and 0.800 for S3 (sensitivity 77.8%, specificity 84.1%). The optimal cut-off CAP values that maximized the Youden index were 250 dB/m ( $\geq$ S1), 299 dB/m ( $\geq$ S2), and 327 dB/m (=S3) respectively.

**Conclusions:** Our data showed that CAP had high diagnostic accuracy for detecting hepatic steatosis in patients with CLD and suggested that CAP is also applicable for Asian patients.

**European Journal of Gastroenterology & Hepatology, 2013- Nov;25(11):1330-1334**

**Noninvasive detection of hepatic steatosis in patients without ultrasonographic evidence of fatty liver using the Controlled Attenuation Parameter evaluated with transient elastography**

Yusuf Yilmaza<sup>c</sup>, Rabia Ergelen<sup>b</sup>, Hakan Akina<sup>c</sup> and Nese Imeryuza<sup>c</sup>

Departments of aGastroenterology, bRadiology, School of Medicine and Institute of Gastroenterology, Marmara University, Istanbul, Turkey

**Objective:** Although ultrasound is a useful technique for detecting hepatic steatosis, it cannot provide a precise determination of hepatic fat content. A novel attenuation parameter named controlled attenuation parameter (CAP) has been developed to process the raw ultrasonic signals acquired by Fibrosan. The aim of this study was to determine the percentage of hepatic steatosis in apparently healthy Turkish individuals using the proposed diagnostic cut-off points for CAP. In addition, we sought to investigate the association of CAP with the traditional risk factors for nonalcoholic fatty liver disease in a screening setting.

**Materials And Methods:** In the present study, 102 Turkish individuals without evidence of fatty liver on ultrasound and normal aminotransferase levels underwent CAP measurements by means of Fibrosan.

**Results:** The mean (SD), median (minimum-maximum), and 5th and 95th percentile values of CAP values in this cohort of 102 individuals were 206.99 (48.12), 210.5 (100.0-314.0), 113.4 and 280.2 dB/m, respectively. Using the cut-offs of 222, 238, and 283



dB/m for CAP, there were 39 (38.2%), 23 (22.5%), and five (4.9%) individuals out of 102 who had at least 10% steatosis despite normal liver findings on ultrasound. After allowance for potential confounders, CAP was independently associated with BMI (beta=0.39, t=3.5, P<0.001) and the number of metabolic syndrome criteria (beta=0.24, t=2.1, P<0.05).

**Conclusion:** These results hold promise for early noninvasive detection of hepatic steatosis on the basis of CAP assessment.

**Kidney Blood Press Res 2013;37:305-310**

**Chronic Kidney Disease and Nonalcoholic Fatty Liver Disease Proven by Transient Elastography**

Ivana Mikolasevic<sup>a</sup>, Sanjin Racki<sup>a</sup>, Ivan Bubic<sup>a</sup>, Ita Jelic<sup>a</sup>, Davor Stimac<sup>b</sup>, Lidija Orlic<sup>a</sup>

*a) Dpt of Nephrology and Dialysis, Division of Internal medicine, University Hospital Center Rijeka, Croatia;*

*b) Dpt of Gastroenterology, Division of Internal Medicine, University Hospital Rijeka, Rijeka, Croatia*

**Background/Aim:** Preliminary data suggest an association between chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD).

The aim of this study was to further investigate the association between NAFLD and decreased kidney function.

**Methods:** A total of 62 patients with CKD were enrolled in the study. Liver stiffness was used to detect liver fibrosis and CAP (controlled attenuation parameter) was used to detect and quantify liver steatosis (FibroScan®). NAFLD was defined by CAP values ≥238 dB.m-1.

**Results:** CKD stage III was present in 29 patients (46.8%) and CKD stage IV in 33 patients (53.2%). Out of 62 CKD patients 53 (85.5%) had NAFLD and of these 14/53 patients (26.4%) had also liver stiffness >7 kPa. The severity of liver steatosis was positively correlated with serum creatinine (r=0.399;p<0.01) and CRP (r=0.261; p<0.05) and negatively correlated with eGFR (r=-0.413; p<0.01) and serum iron concentration (r=-0.365; p<0.01).

**Conclusion:** The results suggest a high prevalence of NAFLD in CKD patients. The severity of liver steatosis is negatively correlated with kidney function. The study documents the value of ultrasonographic elastography as an effective non-invasive screening method for the diagnosis of NAFLD.

**Journal of Gastroenterology & Hepatology, 2013-Jul;28(7):1194-1201**

**Controlled Attenuation Parameter for Non-invasive Assessment of Hepatic Steatosis: Does aetiology affect performance**

Manoj Kumar,\* Archana Rastogi,† Tarandeep Singh,\* Chhagan Behari,† Ekta Gupta,‡ Hitendra Garg,\*Ramesh Kumar,\* Vikram Bhatia\* and Shiv K Sarin\*

*Departments of \*Hepatology, †Pathology and ‡Virology, Institute of Liver and Biliary Sciences, New Delhi, India*

**Background:** Hepatic steatosis is an important parameter to assess in chronic liver disease patients. The

Controlled Attenuation Parameter (CAP) assesses liver steatosis using transient elastography.

**Aim:** To determine the accuracy of CAP for evaluation of hepatic steatosis in chronic hepatitis B virus (CHBV) infected, chronic hepatitis C virus (CHCV) infected and non alcoholic fatty liver disease (NAFLD) patients and to determine the influence of aetiology on the diagnostic accuracy of CAP. **METHODS:** 146 CHBV patients, 108 CHCV infected patients and 63 patients with NAFLD, who underwent both liver biopsy and successful CAP measurements within the study period, were assessed. Area under the Receiver Operating Characteristic (AUROC) was used to evaluate performance of CAP for diagnosing steatosis compared with biopsy.

**Results:** Multivariate analysis found that CAP correlated with BMI [ OR , 95% CI=4.09 (1.2-6.8) for CHBV ; 4.7 (1.1-8.4) for CHCV and 16.2(9.1-24.5) for NAFLD patients respectively] and hepatic steatosis score on biopsy [ OR , 95% CI=30.7 (19.2-42.2)] for CHBV ; 24.2 (11.5-37.3) for CHCV and 21.8(10.1-45.0)16.2(9.1-24.5) for NAFLD patients respectively]. AUROC for CAP was 0.683 (0.601-0.757) for steatosis (S) ≥/6 %, 0.793 (0.718-0.856) for S>33% and 0.841 (0.771-0.896) for S > 66% respectively for CHBV infected patients. There was no difference in accuracy of CAP for assessing liver fat among CHBV, CHCV and NAFLD patients.

**Conclusions:** CAP is a novel, noninvasive tool that can detect and quantify steatosis accurately among CHBV, CHCV and NAFLD patients, the accuracy being similar for all the three groups of patients.

**European Journal of Gastroenterology & Hepatology, 2013 Aug;25(8):905-11**

**Interobserver concordance in Controlled Attenuation Parameter measurement, a novel tool for the assessment of hepatic steatosis on the basis of transient elastography**

Eva Recio<sup>ac</sup>, Celia Cifuentes<sup>ac</sup>, Juan Macías<sup>ac</sup>, José A. Mira<sup>ac</sup>, Manuel Parra-Sánchez<sup>ac</sup>, Antonio Rivero-Juárez<sup>d</sup>, Carmen Almeida<sup>b</sup>, Juan A. Pineda<sup>ac</sup> and Karin Neukam<sup>ac</sup>

*a- Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme,*

*b- Biomedicine Institute of Seville (IBIS),*

*c- Unit of Investigation, Hospital Universitario de Valme, Seville*

*d- Unit of Infectious Diseases, Maimonides Institute for Biomedical Research (IMIBIC), Hospital Universitario Reina Sofía, Cordoba, Spain*

**Background:** the combination of transient elastometry with a Controlled Attenuation Parameter (CAP) is available to evaluate Hepatic Steatosis (HS) along with liver stiffness.

**Aim:** to assess the concordance of CAP measurements between two independent observers in patients infected by HIV and/or hepatitis virus, as well as to determine the concordance of classification of the grade of HS using two cut-off values.

**Materials and methods:** in a cross-sectional prospective study, cap-enabled transient elastometry acquisitions were performed by two independent observers in patients with HIV or hepatitis virus infection. the interobserver concordance between the CAP examinations was assessed using the intraclass

correlation coefficient and the concordance in the classification of patients in the grades of HS was characterized using the  $\kappa$  index.

**Results:** a total of 118 patients were included. twenty (17%) patients were HIV monoinfected, 44 (37.3%) were hepatitis c virus monoinfected, and 52 (44%) had HIV/hepatitis c virus coinfection. the median (q1-q3) of the absolute difference of cap values between the two observers was 20 (10-41) db/m. the overall intraclass correlation coefficient was 0.84 (95% confidence interval: 0.77-0.88). the corresponding figures for liver stiffness measurements were 0.9 (0.4-2.6) kPa and 0.96 (95% confidence interval: 0.94-0.97). the  $\kappa$  indexes for the concordance of classification for the presence of HS, cut-off of 215 db/m, and significant HS, cut-off of 252 db/m, were 0.53 and 0.62, respectively.

**Conclusion:** the determination of HS by means of cap in HIV and/or hepatitis virus infection represents an observer-independent and easily performable method. However, the use of cut-off values for the classification of patients is suboptimal.

**Liver International, 2012 Jul;32(6):911-8**

**Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography**

de Ledinghen V.<sup>1,2</sup>, Vergniol J.<sup>1</sup>, Foucher J.<sup>1</sup>, Merrouche W.<sup>1</sup>, le Bail B.<sup>2-3</sup>

1- Service d'Hépatogastroentérologie, Hôpital Haut-Lévêque, Pessac, France  
2- INSERM U1053, Université Bordeaux Segalen Bordeaux, France  
3- Service d'Anatomie-Pathologique, Hôpital Pellegrin, CHU Bordeaux, Bordeaux, France

**Introduction:** Recently, a study showed that Controlled Attenuation Parameter (CAP), evaluated with transient elastography, could efficiently separate steatosis grades.

**The aim** of this study was to prospectively evaluate the performance of CAP for the diagnosis of steatosis in patients with chronic liver disease.

**Patients and methods:** Consecutive patients with chronic liver disease had steatosis diagnosis using CAP, blood sample and liver biopsy. Steatosis was graded as the percentage of hepatocytes with fat: S0  $\leq$  10%, S1: 11 ~ 33%, S2: 34 ~ 66%, S3  $>$  67%.

**Results:** Characteristics of the 112 patients included were as follows: age 54 years, BMI 26 kg m<sup>-2</sup> (2), HCV 36%, NAFLD 25%. Steatosis repartition was: S0 52%, S1 19%, S2 14%, S3 15%. CAP was significantly correlated with SteatoTest, Fatty Liver Index (FLI), percentage of steatosis on liver biopsy, steatosis grade and slightly with liver stiffness, but not with fibrosis and activity grade on liver biopsy. Using CAP vs SteatoTest vs FLI score, Area Under the Receiver-Operating Characteristics (ROC) curves (AUROC)s were 0.84 vs 0.72 vs 0.72 for the diagnosis of steatosis  $\geq$  S1, 0.86 vs 0.73 vs 0.71 for the diagnosis of steatosis  $\geq$  S2, and 0.93 vs 0.73 vs 0.75 for the diagnosis of steatosis S3 respectively. For a sensitivity  $\geq$  90%, cut-offs of CAP were 215 dB m<sup>-1</sup> for S  $\geq$  1, 252 dB m<sup>-1</sup> for S  $\geq$  2, and 296 dB m<sup>-1</sup> for S3.

**Conclusion:** CAP is very efficient to detect even low grade steatosis. CAP being implemented on FibroScan (Echosens, Paris, France), both steatosis and fibrosis can be evaluated simultaneously, enlarging the spectrum of non-invasive techniques for the management of chronic liver diseases.

**Liver International, 2012 Jul;32(6):902-10**

**Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography**

R. Myers<sup>1</sup>, A. Pollett<sup>2</sup>, R. Kirsch<sup>2</sup>, G. Pomier-Layrargues<sup>3</sup>, M. Beaton<sup>4</sup>, M. Levstik<sup>4</sup>, A. Duarte-Rojo<sup>5</sup>, D. Wong<sup>5</sup>, P. Crotty<sup>1</sup>, M. Elkashab<sup>6</sup>

1- Department of Medicine, University of Calgary, Alberta, Canada  
2- Department of Pathology, Mt. Sinai Hospital Toronto, Ontario, Canada  
3- Liver Unit, Hôpital Saint-Luc, Montréal, Québec, Canada  
4- Multi-Organ Transplant Unit, University of Western Ontario, London, Ontario, Canada  
5- Toronto Western Hospital Liver Centre, Toronto, Ontario, Canada  
6- The Toronto Liver Centre, Toronto, Ontario, Canada

**Background:** Accurate tools for the noninvasive detection of hepatic steatosis are needed. The Controlled Attenuation Parameter (CAP) specifically targets liver steatosis using a process based on transient elastography.

**Methods:** Patients with chronic liver disease and body mass index (BMI)  $\geq$  28 kg/m<sup>2</sup> underwent biopsy and liver stiffness measurement (LSM) with simultaneous CAP determination using the FibroScan<sup>®</sup> M probe. The performance of the CAP for diagnosing steatosis compared with biopsy was assessed using areas under receiver operating characteristic curves (AUROC).

**Results:** A total of 153 patients were included: 69% were male, median BMI was 32 kg/m<sup>2</sup>; 47% had nonalcoholic fatty liver disease (NAFLD); and 65% had significant ( $\geq$  10%) steatosis. The CAP was significantly correlated with the percentage of steatosis ( $\rho = 0.47$ ) and steatosis grade ( $\rho = 0.51$ ; both  $P < 0.00005$ ). The median CAP was higher among patients with significant steatosis (317 [IQR 284–339] vs. 250 [227–279] dB/m with  $<$ 10% steatosis;  $P < 0.0005$ ) and the AUROC for this outcome was 0.81 (95% CI 0.74–0.88). At a cut-off of 283 dB/m, the CAP was 76% sensitive, 79% specific, and had positive and negative predictive values of 87% and 64%, respectively. CAP performance was not influenced by measurement variability, but was higher in patients with mild (F0-F1) fibrosis (AUROC 0.89 vs. 0.72 with F2-F4;  $P = 0.03$ ). The AUROCs of the CAP for  $\geq$  5%,  $>$  33% and  $>$  66% steatosis were 0.79, 0.76 and 0.70, respectively.

**Conclusions:** The CAP is a promising tool for the noninvasive detection of hepatic steatosis. Advantages of CAP include its ease of measurement, operator-independence and simultaneous availability with LSM for fibrosis assessment.

**Journal of Viral Hepatitis, 2012 Apr;19(4):244-53**

**Novel Controlled Attenuation Parameter (CAP) for noninvasive assessment of steatosis using Fibroscan®: validation in chronic hepatitis C**

M. Sasso<sup>1</sup>, Tengher-Barna<sup>2</sup>, M. Ziol<sup>2</sup>, V. Miette<sup>1</sup>, C. Fournier<sup>3</sup>, L. Sandrin<sup>1</sup>, R. Poupon<sup>4</sup>, A.-C. Cardoso<sup>5</sup>, P. Marcellin<sup>5</sup>, C. Douvin<sup>6</sup>, V. de Ledinghen<sup>7</sup>, J.-C. Trinchet<sup>8</sup>, M. Beaugrand<sup>8</sup>

- 1- R&D Department, Echosens, Paris, France
- 2- Department of Pathology, Hôpital Jean Verdier, AP-HP and Paris 13 University, Bondy
- 3- Medical Affairs Department, Echosens, Paris, France
- 4- Hôpital Saint-Antoine, Paris, France
- 5- Hôpital Beaujon, Clichy, France
- 6- Hôpital Henri Mondor, Creteil, France
- 7- Hôpital Haut-Lévêque, Bordeaux, France
- 8- Department of Hepatology Hôpital Jean Verdier, Bondy, France

**Background & Aims:** A novel Controlled Attenuation Parameter (CAP) has been developed for Fibroscan® to assess liver steatosis, simultaneously with liver-stiffness measurement (LSM). We assessed for the first time CAP diagnostic accuracy in a large cohort of patients with chronic hepatitis C virus (CHC), together with LSM.

**Methods:** 615 patients with CHC, who underwent both Fibroscan® and liver biopsy were analyzed. Fibrosis was graded using METAVIR score. Steatosis was categorized by visual assessment as S0: steatosis in <10% of hepatocytes, S1: 11–33%, S2: 34–66%, and S3: 67–100%. Performances of CAP and LSM were determined using receiveroperating characteristic (ROC) curve analysis and cross-validated using the bootstrap method. The Obuchowski measure was used to assess overall accuracy of CAP and to differentiate between steatosis grades.

**Results:** In multivariate analysis, CAP was related to steatosis (p<10<sup>-15</sup>) independently of fibrosis stage (which was related to LSM). The areas under ROC curves (AUROC) using CAP to detect steatosis, were 0.80 (95% CI, 0.75–0.84) for S≥S1, 0.86 (0.81–0.92) for S≥S2 and 0.88 (0.73–1) S=S3. CAP exhibited a good ability to differentiate steatosis grades (Obuchowski measure = 0.92). Performance of LSM for fibrosis assessment confirmed results from previous studies.

**Conclusions:** CAP is a novel tool to assess the degree of steatosis. CAP was independently validated for the first time in a cohort of patients with CHC and show good diagnostic performance. Both fibrosis and steatosis can be evaluated noninvasively during the same procedure using Fibroscan®, in patients with CHC.

**Clinics & Research in Hepatology & Gastroenterology, 2012 Feb;36(1):13-20**

**The controlled attenuation parameter (CAP): A novel tool for the non-invasive evaluation of steatosis using Fibroscan**

M. Sasso<sup>1</sup>, V. Miette<sup>1</sup>, L. Sandrin<sup>1</sup>, M. Beaugrand<sup>2</sup>

- 1- R&D Department, Echosens, Paris, France
- 2- Department of Hepatology Hôpital Jean Verdier, Bondy, France

Steatosis is a reversible and benign condition. However, in a few cases, steatosis is associated with inflammation and hepatocyte changes, and is then defined as steato-hepatitis. Steatosis can also be a co-

factor in many chronic liver diseases that can lead to fibrosis and cirrhosis. Although an important parameter, until now, evaluation of steatosis by non-invasive methods has remained challenging. In this paper, we report on the use of a novel non-invasive methodology called a controlled attenuation parameter (CAP). This is based on signals acquired by the Fibroscan, which was developed to specifically assess liver steatosis concomitant to liver stiffness measurements (LSM). CAP's performance from published articles and communications is also reported.

**Ultrasound in Medicine & Biology, 2010 Nov;36(11):1825-35**

**Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis - Preliminary study and validation in a cohort of patients with chronic liver disease from various causes**

M. Sasso<sup>1</sup>, M. Beaugrand<sup>2</sup>, V. de Lédighen<sup>3</sup>, C. Douvin<sup>4</sup>, P. Marcellin<sup>5</sup>, R. Poupon<sup>6</sup>, L. Sandrin<sup>1</sup>, V. Miette<sup>1</sup>

- 1- R&D Department, Echosens, Paris, France
- 2- Hôpital Jean Verdier, Bondy, France
- 3- Hôpital Haut-Lévêque, Bordeaux, France
- 4- Hôpital Henri Mondor, Creteil, France
- 5- Hôpital Beaujon, Clichy, France
- 6- Hôpital Saint-Antoine, Paris, France

There is a need for noninvasive methods to detect liver steatosis, which can be a factor of liver fibrosis progression. This work aims to evaluate a novel ultrasonic controlled attenuation parameter (CAP) devised to target, specifically, liver steatosis using a sophisticated process based on Vibration Control Transient Elastography (VCTE). CAP was first validated as an estimate of ultrasonic attenuation at 3.5 MHz using Field II simulations and tissue-mimicking phantoms. Performance of the CAP was then appraised on 115 patients, taking the histological grade of steatosis as reference. CAP was significantly correlated to steatosis (Spearman r = 0.81, p, 10216). Area under receiver operative characteristic (ROC) curve (AUC) was equal to 0.91 and 0.95 for the detection of more than 10% and 33% of steatosis, respectively. Furthermore, results show that CAP can efficiently separate several steatosis grades. These promising results suggest that CAP is a noninvasive, immediate, objective and efficient method to detect and quantify steatosis.

COMMUNICATIONS

Poster EASL 2014 (Apr 9-13)

**Liver steatosis assessment with CAP at 3.5 Mhz using FibroScan M and XL Probe**

V. de Ledinghen<sup>1</sup>, C. Corpechot<sup>2</sup>, J. Vergniol<sup>1</sup>, P. Bedossa<sup>3</sup>, O. Chazouilleres<sup>2</sup>, Y. Menu<sup>4</sup>, V. Paradis<sup>3</sup>

1- Hepato-gastroenterology, Haut Leveque Hospital, Pessac,  
 2- Hepato-gastroenterology, Saint Antoine Hospital, Paris,  
 3- Pathology, Beaujon Hospital, Clichy,  
 4- Radiology, Saint Antoine Hospital, Paris, France

**Background and aims:** Controlled Attenuation Parameter (CAP) measures liver ultrasound attenuation at 3.5 MHz using FibroScan (FS). Currently available on the M probe to quantify steatosis, the aim of this work was to implement the measurement of CAP on the XL probe (dedicated to overweighted patients) and validate its diagnosis performance.

**Methods:** 180 consecutive patients (21% NAFLD, 25% VHC, 14 % VHB, and 40% other - BMI=25±11kg/m<sup>2</sup>, age=51±15years, 53% male) with histological assessment of steatosis within 7 days of FS (liver biopsy≥15 mm, double-blind reading) were enrolled. Steatosis was graded and distributed as follows: S0: steatosis≤10% (63%), S1: 11~33% (11%), S2: 34~66% (10%), S3: ≥67% (16%). Spearman correlation coefficient (SCC), intra-class correlation coefficient (ICC), Area under Receiver Operating Characteristic curve (AUROC) and Delong-test for comparison of AUROC were used to analyse the data.

**Results:** SCC of CAP with histological steatosis was 0.65 and 0.64 for XL and M probes respectively. The AUROCs (area under ROC curve) of CAP at 3.5 MHz versus histological steatosis (Table 1) were not significantly different when measured by either the M or the XL probe and cut-off maximizing the Youden index for the M probe had similar performance for CAP measured with XL probe.

**Conclusions:** Measurement of CAP at 3.5 MHz is feasible in with the FS XL probe and therefore in overweighted patients for whom steatosis is more prevalent. This work confirms that the diagnosis accuracy of CAP for steatosis assessment is equivalent when using either the M or the XL probe.

Steatosis		M Probe	XL Probe
≥ 11 % (n=66 - 37%)	AUROC ± SD	0.832 ± 0.034	0.836 ± 0.033
	Cut-off	267 dB/m	
	Sensitivity	68.2	66.7
	Specificity	86.0	89.5
≥ 34 % (n=47 - 26%)	AUC ± SD	0.895 ± 0.032	0.900 ± 0.031
	Cut-off	272 dB/m	
	Sensitivity	82.9	82.9
	Specificity	87.9	87.2
≥ 67 % (n=29 - 16%)	AUC ± SD	0.945 ± 0.017	0.949 ± 0.019
	Cut-off	290 dB/m	
	Sensitivity	86.2	89.7
	Specificity	84.7	86.8

Table 1

Poster EASL 2014 (Apr 9-13)

**Predictors of hepatic steatosis in a prospective study of European untreated hepatitis b surface antigen (HBSAG) carriers: evaluation by Controlled Attenuation Parameter (CAP)**

V. Knop, J. Vermehren, M. Friedrich-Rust, T. Welzel, D. Fitting, S. Susser, C. Füller, S. Zeuzem, C. Sarrazin  
 Klinikum der J. W. Goethe-Universität, Frankfurt, Frankfurt, Germany

**Background and aims:** Little is known about the relevance of hepatic steatosis in HBsAg carriers in the European population. Recently, a novel controlled attenuation parameter (CAP) has been designed for ultrasound-based noninvasive assessment of steatosis. The aim of the present study was to prospectively perform CAP measurement to investigate predictors of steatosis in a cohort of European untreated HBsAg carriers.

**Methods:** 123 HBsAg carriers who were part of a multicentric prospective cohort were referred to liver stiffness measurement simultaneously with CAP. Elevated ALT levels (ALT>ULN) were detected in 14/123 patients, whereas 8/123 had elevated GGT values (GGT>ULN). Steatosis was categorized by using the following cut-offs: grade 0:< 222 dB/m, grade 1:222-232 dB/m, grade 2:233-289 dB/m, grade 3:>289 dB/m. Biochemical, virological and metabolic factors were compared.

**Results:** In 16 patients CAP-measurement failed due to obesity. In the remaining 107 HBsAg carriers CAP detected grade 0 in 36, grade 1 in 13, grade 2 in 38, and grade 3 steatosis in 20 patients. Higher BMI, lower HDL (p< 0.002) and higher age (p< 0.004) were associated with steatosis. In the subgroup of patients with elevated liver enzymes, 9/13 (ALT>ULN) and 7/8 (GGT>ULN) had documented steatosis by CAP. Taking into account only patients with HBV-DNA< 1000U/ml, 6/7 (ALT>ULN) and 5/5 (GGT>ULN) had increased CAP.

**Conclusions:** Steatosis was mainly associated with metabolic factors in our cohort of HBsAg carriers, whereas virological parameters and fibrosis stage had no influence. In the subgroup of patients with HBV-DNA< 1000U/ml, steatosis and metabolic determinants, but not viral factors, were correlated with elevated liver enzymes.

Poster EASL 2014 (Apr 9-13)

**Patients with T2DM accompanying severe degree of NAFLD assessed by Controlled Attenuation Parameter using FibroScan**

Y.E. Chon<sup>1</sup>, K. Kim<sup>2</sup>, K.S. Jung<sup>1</sup>, S.U. Kim<sup>1</sup>, J.Y. Park<sup>1</sup>, D.Y. Kim<sup>1</sup>, S.H. Ahn<sup>1</sup>, C.Y. Chon<sup>1</sup>, K.-H. Han<sup>1</sup>

1- Department of Internal Medicine, Institute of Gastroenterology,  
 2- Department of Internal Medicine, Institute of Endocrinology, Yonsei University College of Medicine, Seoul, Republic of Korea

**Background and aims:** The high prevalence of hepatic steatosis in diabetic population is well known. However, the severity of hepatic steatosis in diabetic population compared to that of normal or prediabetic population has not yet been assessed, and whether there is a



difference in the degree of steatosis between these groups is not known.

**Methods:** Subjects who underwent laboratory tests for T2DM and CAP using Fibrosan® as a regular health check-up were enrolled. CAP value 250dB/m was selected as a cutoff for presence of steatosis, and CAP value 300dB/m for moderate to severe steatosis. Biomarkers related to T2DM included fasting glucose, fasting insulin, C-peptide, HbA1c, glycoalbumin, HOMA-IR, HOMA-β, and hs-CRP.

**Results:** Among 340 study participants (T2DM,n=66; pre-diabetes,n=202; normal glucose tolerance,n=72), the proportion of subjects with steatosis increased according to the glucose tolerance status (31.9% in normal glucose tolerance; 47.0% in pre-diabetes; 57.6% in T2DM). The median CAP value was significantly higher in patients with T2DM (265dB/m) compared to those with pre-diabetes (245dB/m) or normal glucose tolerance (231dB/m) (all P< 0.05). Logistic regression analysis showed that subjects with moderate to severe steatosis had a 2.1-fold higher risk of having T2DM compared to those without steatosis(P=0.02; OR=2.4;95% CI=1.1-4.9), and positive correlations between the CAP value with HOMA-IR(ρ=0.407) and C-peptide(ρ=0.402) were clearly demonstrated.

**Conclusions:** This study has found that hepatic steatosis is not only a risk factor of diabetes, but that diabetes itself is associated with more severe degree of steatosis. The increasing severity of hepatic steatosis in diabetic subjects may be due to insulin resistance.

#### Poster EASL 2014 (Apr 9-13)

##### The Common PNPLA3 Variant is associated with hepatic steatosis quantified by Controlled Attenuation Parameter and determines the fate of patients with chronic liver diseases

A. Arslanow, C.S. Stokes, S.N. Weber, F. Grünhage, F. Lammert, M. Krawczyk

*Department of Medicine II, Saarland University Medical Center, Homburg/Saar, Germany*

**Background and aims:** The common variant p.I148M of the PNPLA3 gene encoding the enzyme adiponutrin represents a genetic driver of severe hepatic phenotypes (Anstee/Day Nat Rev Gastroenterol Hepatol 2013). Here we present the results in patients with chronic liver diseases (CLD) who were referred to our center between 2010 and 2013 for genotyping of PNPLA3 as a part of their diagnostic work-up.

**Methods:** The PNPLA3 SNP rs738409G>C (p.I148M) was genotyped by Taqman assays in 234 patients with CLD (133 men; 180 with non-viral liver diseases; 14 - 77 years). Liver steatosis was measured non-invasively using controlled attenuation parameter (CAP™) in a subgroup of 97 patients. The control cohort consisted of 279 healthy individuals (114 men; 32 - 98 years).

**Results:** The PNPLA3 variant increased the odds of presenting with severe liver phenotypes that eventually lead to referral and informed consent for genotyping (common OR = 1.72, P 0.001). Median CAP [dB/m] levels

differed significantly (ANOVA P = 0.0025) between carriers of the genotypes [II] (n = 46), [IM] (n = 40) and [MM] (n = 11) and were 246.0, 277.0 and 320.0, respectively. Carriers of the prosteatotic [M] allele had higher (P = 0.0043) median CAP levels as compared to the [II] individuals.

**Conclusions:** This is the first study showing an association between hepatic steatosis quantified using CAP and the PNPLA3 variant across various liver diseases. Our results provide evidence that patients with the PNPLA3 risk variant develop more severe liver diseases, supporting the concept of PNPLA3-associated steatohepatitis (PASH;Semin Liver Dis 2013).

#### Poster EASL 2014 (Apr 9-13)

##### Non-invasive characterization of post-transplant fatty liver disease reveals high prevalence of graft injury in association with metabolic syndrome, recipient PNPLA3 genotype and alcoholic liver cirrhosis

T. Karlas<sup>1,2</sup>, J. Kollmeier<sup>2</sup>, S. Böhm<sup>3</sup>, J. Müller<sup>4</sup>, M. Tröltzsch<sup>2</sup>, A. Weimann<sup>5</sup>, M. Bartels<sup>5</sup>, J. Rosendahl<sup>2</sup>, J. Mössner<sup>2</sup>, T. Berg<sup>3</sup>, V. Keim<sup>2</sup>, J. Wiegand<sup>2</sup>

*1- IFB Adiposity Diseases Leipzig, Leipzig University Medical Center,*

*2- Department of Internal Medicine, Dermatology & Neurology, Division of Gastroenterology & Rheumatology,*

*3- Department of Internal Medicine, Dermatology and Neurology, Division of Gastroenterology & Rheumatology; Section of Hepatology,*

*4- Department of Diagnostic & Interventional Radiology,*

*5- Dpt of Visceral Surgery & Transplantation, University Hospital Leipzig, Germany*

**Background and aims:** Hepatic steatosis contributes to liver graft injury and impaired long-term outcome, but data on the prevalence of post-transplant fatty liver disease (FLD) are limited. We therefore performed a comprehensive non-invasive evaluation of post-transplant FLD and associated risk factors.

**Methods:** 204 liver transplant recipients (n=102 non-alcoholic etiology, non-ALC; n=102 alcoholic liver disease, ALC; 42% female; age median/range 57.8/19.1-79.9 years; time since transplantation 66/2-242 months) underwent transient elastography (TE), Controlled Attenuation Parameter (CAP), ultrasound, and NAFLD fibrosis score assessment. Recipient DNA samples were genotyped for PNPLA3 (rs738409), and IL28B (rs8099917,rs12979860) polymorphisms.

**Results:** Valid elastography results and genotyping were available in 157 and 196 cases, respectively. 43% of patients were overweight and 20% obese. 74/204 displayed increased hepatic echogenicity at ultrasound, in 71/157 and 37/157 CAP indicated steatosis (>245dB/m) and advanced steatosis (>300 dB/m), respectively. PNPLA3 non-CC genotype was associated with increased CAP (257/100-400 vs. 222/100-354 dB/m, p=0.032), higher liver stiffness (TE 6.4/2.6-74 vs. 5.5/2.4-53 kPa, p=0.005), and diabetes mellitus frequency (39% vs. 22%, p=0.013). IL28B rs12979860 non-CC genotype was associated with higher BMI and TE values, while no association was observed for rs8099917.

ALC patients had higher diabetes mellitus (41% vs. 25%, p=0.017) and PNPLA3 non-CC prevalences (73% vs.



47%,  $p=0.005$ ), and higher BMI values ( $28.2\pm 4.6$  vs.  $25.6\pm 4.4$  kg/m<sup>2</sup>,  $p < 0.001$ ). Median liver stiffness ( $p=0.022$ ), CAP ( $p=0.001$ ) and NAFLD score ( $p < 0.001$ ) were elevated in the ALC cohort.

**Conclusions:** Modern ultrasound assessment frequently detects post-transplant FLD, which is associated with components of the metabolic syndrome and recipient PNPLA3 non-CC genotype, especially in ALC patients.

**Poster AASLD 2013 (Nov 1<sup>st</sup>-5)**

**Liver steatosis, presumed by SteatoTest or Controlled Attenuation Parameter (CAP), is associated to a risk of false-positive liver stiffness measurement by transient elastography in type-2 diabetic patients**

Hugo Perazzo<sup>1,2</sup>, Yen Ngo<sup>3</sup>, Mona Munteanu<sup>3</sup>, Noemi Seurat<sup>1</sup>, Elena Luckina<sup>1</sup>, Fanny Rutka<sup>4</sup>, Marion Coureau<sup>4</sup>, Sophie Jacqueminet<sup>5</sup>, Denis Monneret<sup>4</sup>, Françoise Imbert-Bismut<sup>4</sup>, Vlad Ratziu<sup>1</sup>, Agnes Hartemann-Heurtier<sup>5</sup>, Thierry Poynard<sup>1</sup>

1. Hepatology, APHP UPMC Liver center, Pitié-Salpêtrière Hospital, Paris, France

2. Inserm U938, Paris, France

3. BioPredictive, Paris, France

4. Biochemistry, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

5. Diabetology, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

**Background:** Transient elastography (TE) with Controlled Attenuation Parameter (CAP), based on liver stiffness measurement (LSM); FibroTest (FT), ActiTest (AT) and SteatoTest (ST) are validated non-invasive alternative to assess liver injury in NAFLD-risk patients as type-2 diabetics (T2D). Necro-inflammatory activity and steatosis might influence LSM leading to overestimation fibrosis stages.

**Aims:** To evaluate the impact of i steatosis (SS) [ $>32\%$ ] on LSM in T2D patients.

**Methods:** 142 T2D, without liver disease history, screened for fibrosis with FT were reinvestigated by FT and LSM (M and XL probes) after a median delay of 7 years. Patients with minimal fibrosis ( $FT < 0.48$ -FOF1 METAVIR) at baseline and without progression during follow-up were included. Exclusion criteria were presence of advanced fibrosis (AF) [ $FT \geq 0.48$ ] or activity [ $AT \geq 0.27$ ] at the reinvestigation. Patients without AF as per FT ( $< 0.48$ ), but with AF LSM  $\geq 7.1$  kPa, at the reinvestigation, were supposed as false-positive of LSM (FP-LSM). SS ( $>32\%$ ) was defined as per ST  $\geq 0.69$  or CAP  $\geq 283$  dB/m.

**Results:** 106 T2D patients with minimal fibrosis in the last 7 yrs and without necro-inflammatory activity were pre-included [54% males, age 63 yrs, median BMI  $27.6(20.8-52.8)$  Kg/m<sup>2</sup>, ALT  $23(10-59)$  U/L]. After exclusion of non-applicable LSM by both probes (6.6%), 99 patients were analyzed. Patients supposed to be a LSM-FP (26%) had no liver-related complications. In univariate analysis, patients considered as FP-LSM versus non-FP-LSM, had higher: BMI [ $32.3(21.3-49.5)$  vs  $26.5(19.6-35.2)$ ], ST ( $0.64\pm 0.17$  vs  $0.46\pm 0.19$ ); waist circumference ( $115\pm 18$  vs  $100\pm 11$  cm), thoracic fold ( $25\pm 10$  vs  $19\pm 6$  mm)

and higher rates of SS (58% vs 19%), all  $p < 0.001$ . SS patients as per ST, had higher median LSM (range) [ $7.7(5-75)$  vs  $5.5(3-64)$ ,  $p=0.02$ ]. In logistic regression, the presence of SS, by ST [OR =  $6.9(95\%CI 1.7-28.4)$ ;  $p=0.007$ ], remained significantly associated to FP-LSM in a multivariate model adjusted for age, gender, thoracic fold, waist circumference and metabolic factors. Among 59 patients with an applicable CAP simultaneous to ST, Spearman's correlation coefficient was  $r=0.37$ ,  $p=0.03$ . Supposed FP-LSM patients had also higher rates of SS by CAP (40% vs 15%,  $p=0.04$ ) compared to non-FP-LSM. Patients with SS as per CAP, had higher median LSM [ $6.5(4.4-13.6)$  vs  $5.7(3.2-8.7)$  kPa,  $p=0.01$ ]. The high failure rate (35%) of the M probe that measures concomitantly the CAP, limited the multivariate analysis for CAP in this population.

**Conclusion:** In type-2 diabetic patients, the presence of severe steatosis presumed by SteatoTest was independently associated to the overestimation of liver fibrosis by liver stiffness measurement.

**Poster AASLD 2013 (Nov 1<sup>st</sup>-5)**

**Comparison between results of hepatic transient elastography (FibroScan®) and Controlled Attenuation Parameter (cap™) versus liver biopsy in NAFLD Patients**

Rabelo<sup>1</sup>, José Tadeu Stefano<sup>1</sup>, Flair J. Carrilho<sup>1</sup>

1. Gastroenterology, University of São Paulo School of Medicine, São Paulo, São Paulo, Brazil

**Background and aims:** The aim of this study was to compare the results of FibroScan® and CAP™ versus liver biopsy in patients with Non Alcoholic Fatty Liver Disease (NAFLD).

**Methods:** We enrolled patients with NAFLD diagnosed by liver biopsy between May of 2011 and January of 2013 at Sao Paulo University Hospital. They underwent liver stiffness measurements to assess fibrosis by FibroScan® using median and extra large probes according to their skin-liver distance. CAP™ was also used to assess steatosis when FibroScan® measures were made with the median probe. The FibroScan® was operated by 2 experts in the procedure. The time frame between liver biopsy and FibroScan® plus CAP™ was of sixty days at most. We considered failure of FibroScan® and CAP™ when: we couldn't have ten valid measures; the total success rate was below 60% and/or the interquartile range (IQR) was above 30%. The results of these noninvasive methods were compared with liver histology (BRUNT criteria), used as the reference standard. The corresponding values of FibroScan® (kPa) to fibrosis stages and of CAP™ (dBm-1) to steatosis grades considered were based in previous studies of these methods in NAFLD patients. The gamma distribution function was used to compare the results of FibroScan® and CAP™ versus liver biopsy.

**Results:** A total of 65 patients were enrolled, 71% female and 29% male with mean age of 56 years old (13-71 years). Mean body mass index (BMI) and abdominal circumference were  $31.29$  Kg/m<sup>2</sup> ( $19.6-47.7$  Kg/m<sup>2</sup>) and

102.3cm (77-135cm), respectively. Mean distance between skin surface and liver was 2.06cm (0.98-4.26cm). Patient's comorbidities were: 46% diabetes; 73% dyslipidemia; 60% systemic arterial hypertension. The FibroScan® was feasible in 83 % (95%CI: 0.7193 – 0.9039) of a total of 65 patients and CAP™ was feasible in 74% (95%CI: 0.603 – 0.848) of a total of 47 patients, respectively. The results of comparison between FibroScan®, CAP™ and liver biopsy (noninvasive methods evaluated separately) using gamma distribution function were: FibroScan® gamma= 0.38(95%CI 0.09-0.66) and CAP™ gamma= 0.46(95%CI 0.06-0.85).

**Conclusions:** FibroScan® and CAP™ were feasible in most of NAFLD patients studied. However, the agreement of these noninvasive methods when compared to liver histology was unsatisfactory. Besides the prevalence of high BMI, perhaps the heterogeneous fibrosis and steatosis of NAFLD liver histology were to blame.

**Poster APASL 2013 (June 6-10)**

**Influencing Factors and Reproducibility of Controlled Attenuation Parameters (CAP) in the Evaluation of Fatty Liver Disease Using FibroScan**

Feng Shen, Jian-Gao Fan, Zheng-Jie Xu

*Gastroenterology, School of Medicine, Shanghai Jiaotong University, Shanghai, China*

**Objective:** To evaluate the influencing factors and reproducibility of controlled attenuation parameters (CAP) measurement of fatty liver using FibroScan.

**Methods:** Patients with non-alcohol fatty liver disease (NAFLD) and normal controls were recruited to complete the CAP measurement with new FibroScan-502 and M probe. In NAFLD groups, some subjects were repeatedly checked-up by the same or different operator. Intraclass correlation coefficient (ICC) was used to evaluate the reproducibility of the operation.

**Results:** A total of 228 subjects were recruited, and 200 subjects (87.7%) got the valid measurement; the success rates in normal and obese persons were 93.9% (77/82) and 75.0% (33/44,  $\chi^2 = 9.548$ ,  $P = 0.02$ ), respectively; female, senior and obese persons had lower success of examination; CAP values in NAFLD group was 291.1±54.0 dB/m, significantly higher than that in control groups (216.4 ± 43.3 dB/m,  $P < 0.01$ ); The ICC was 0.848 (95% CI 0.761~0.905,  $P < 0.01$ ) with same operator and 0.718(95% CI 0.607~0.896,  $P < 0.01$ ) with different operator.

**Conclusion:** The CAP can be used for non-invasive diagnosis of fatty liver, with a good reproducibility.

**Poster APASL 2013 (June 6-10)**

**A Promising Clinical Utility of the Controlled Attenuation Parameter (CAP) for Noninvasive Assessment of Steatosis Using Fibroscan**

Harry Yoon<sup>1</sup>, Hana Park<sup>1</sup>, Suk Pyo Shin<sup>2</sup>, Kyu Sung Rim<sup>1</sup>, Seong Gyu Hwang<sup>1</sup>

*1-Department of Internal Medicine, Institute of Gastroenterology, CHA Bundang Medical Center, CHA University, Seongnam-si*

*2-Department of Internal Medicine, Institute of Gastroenterology, CHA Bundang Medical Center, CHA University, Sung Nam, Republic of Korea*

The CAP (controlled attenuation parameter) based on Fibroscan® has been recently developed for the evaluation of steatosis by non-invasive method. In this study, we aim to report the usefulness of CAP for the assessment of steatosis.

482 patients with chronic liver disease underwent liver stiffness measurement (LSM) with simultaneous CAP determination using the Fibroscan® were included. Sonographic steatosis grade was assessed by one expert physician blinded to CAP, and compared with the steatosis grades based on CAP.

Characteristics of the 482 patients included were as follow: male 289 (60%), median age 46.43±11.20 years, BMI 21.62±8.01 kg/m<sup>2</sup>. Clinical and laboratory variables were well stratified according to the steatosis grades based on CAP, and there were statistically significant differences of body weight, BMI, serum alanine aminotransferase level and serum triglyceride level among the grades. CAP showed positive correlation with body weight ( $r=0.427$ ,  $p < 0.001$ ) and BMI ( $r=0.407$ ,  $p < 0.001$ ). Although sequential differences of CAP depending on the sonographic steatosis grades were revealed (diffuse liver disease/normal = 221.71 ± 47.05dB/m; mild fatty liver = 244.54±47.14 dB/m; moderate fatty liver = 294.56±44.68 dB/m; severe fatty liver = 320.71±48.46 dB/m,  $p < 0.001$ ), there were discordances of steatosis grades between those based on sonography and CAP.

The CAP is a promising tool for the noninvasive detection of hepatic steatosis. Advantages of CAP include its ease of measurement, simultaneous availability with LSM for fibrosis assessment, and provision of additional objective information to the sonographic diagnosis of steatosis.

**Poster APASL 2013 (June 6-10)**

**Noninvasive Detection of Hepatic Steatosis in Subjects without Ultrasonographic Evidence of Fatty Liver Using the Controlled Attenuation Parameter (CAP)**

Yusuf Yilmaz<sup>1,2</sup>, Rabia Ergelen<sup>3</sup>, Hakan Akin<sup>1,2</sup>, Nese Imeryuz<sup>1,4</sup>

*1-Department of Gastroenterology, Marmara University, School of Medicine,*

*2-Institute of Gastroenterology, Marmara University,*

*3-Department of Radiology, Marmara University, School of Medicine,*

*4-Institute of Gastroenterology, Marmara University, Istanbul, Turkey*

**Background/aims:** Although ultrasound is a useful technique for detecting hepatic steatosis, it is unable to provide a precise determination of hepatic fat content. A novel attenuation parameter named Controlled Attenuation Parameter (CAP) has been developed to process the raw ultrasonic signals acquired by the Fibroscan, which is an ultrasound-based device used to diagnose liver disease. This study was designed to determine the prevalence of hepatic steatosis in apparently healthy Turkish subjects with CAP using the proposed diagnostic cutoffs. In addition, we sought to

investigate the association of CAP with the traditional risk factors for NAFLD in a screening setting.

**Methods:** A total of 102 Turkish subjects without evidence of fatty liver on ultrasound and normal aminotransferase levels (64 females and 38 males, mean age  $35 \pm 9$  years) underwent CAP measurements by means of Fibroscan. Patients with a diagnosis of the metabolic syndrome (MS) were excluded.

**Results:** The mean (standard deviation), median (minimum–maximum), and 5th and 95th percentile values of CAP values were 206.99 (48.12), 210.5 (100.0–314.0), 113.4, and 280.2 dB/m, respectively. Therefore, the normal range of CAP in our population was 113.4–280.2 dB/m. By using the cutoffs of 222 dB/m, 238 dB/m, and 283 dB/m for CAP, there were 39 (38.2%), 23 (22.5%), and 5 (4.9%) subjects who had  $\geq 10\%$  steatosis despite normal ultrasound findings. CAP was independently associated with body mass index (beta = 0.39,  $t = 3.5$ ,  $P < 0.001$ ) and the number of MS criteria (beta = 0.24,  $t = 2.1$ ,  $P < 0.05$ ).

**Conclusions:** These results hold promise for early noninvasive detection of hepatic steatosis based on CAP assessment. Because the presence of macrovesicular steatosis is associated with an increased risk of graft loss, our results may stimulate further studies on the usefulness of CAP for selecting living-related donor livers in a transplantation setting.

**Poster EASL 2013 (April 24-28)**

**Interobserver concordance in Controlled Attenuation Parameter (CAP) measurement, a novel tool for the assessment of hepatic steatosis based on transient elastography**

E. Recio<sup>1</sup>, K. Neukam<sup>1</sup>, C. Cifuentes<sup>1</sup>, M. Mancebo<sup>1</sup>, J. Macías<sup>1</sup>, C. Almeida<sup>2</sup>, N. Merchante<sup>1</sup>, J.A. Mira<sup>1</sup>, A. Rivero-Juárez<sup>3</sup>, J.A. Pineda<sup>1</sup>

*1) Unit of Infectious Diseases and Microbiology, 2) Unit of Investigation, Hospital Universitario de Valme, Seville, 3) Unit of Infectious Diseases, Maimonides Institute for Biomedical Research (IMIBIC), Hospital Universitario Reina Sofía, Córdoba, Spain*

**Introduction:** The combination of transient elastometry (TE) with controlled attenuation parameter (CAP) allows non-invasive measurements of hepatic steatosis (HS) simultaneously to liver stiffness. TE is characterized by a high reproducibility and low inter-observational variability in HCV-infected patients with or without HIV coinfection. Nevertheless, no data are available on interobserver differences in CAP values. This is a relevant point, since HS is a very common disorder among HIV-infected patients, and accurate non-invasive diagnosis is critical.

**Objective:** To assess the concordance of CAP measurements between two independent observers in patients infected with HIV and/or hepatitis virus.

**Methods:** In a cross-sectional, prospective study conducted from December 2011 to March 2012 in a university hospital in Spain, CAP-enabled TE acquisitions were performed by two independent observers in 118 consecutive patients with HIV and/or hepatitis virus

infection. The interobserver concordance between the CAP value measurements was assessed using the intraclass correlation coefficient (ICC) and the concordance of the classification of patients regarding the grades of HS was characterized using the kappa index. Patients with CAP  $\geq 238$  dB/m were considered to bear significant HS ( $\geq 10\%$  hepatocytes involved), as previously reported.

**Results:** 78% patients were male. Twenty (17%) patients were HIV monoinfected, 44 (37.3%) hepatitis C virus (HCV)-monoinfected and 52 (44%) showed HIV/HCV coinfection. The median (Q1-Q3) values of CAP obtained by the first and the second observer were 228 (205-265) and 227 (196-269) dB/m, respectively. The median (interquartile range) of the absolute difference of CAP values between the two observers was 20 (10-41) dB/m. The overall ICC was 0.84 (95% confidence interval: 0.77-0.88). The kappa index for the concordance of classification for the presence of significant HS was 0.55. No factor was associated with a greater concordance between observers.

**Conclusions:** The concordance of CAP values obtained by two observers is good. Therefore, the determination of HS by means of CAP in HIV and/or hepatitis virus infection represents an observer-independent and easily performable method. However, the concordance of the diagnosis of significant HS, defined by the cutoff of 238 dB/m, is suboptimal.

**Poster EASL 2013 (April 24-28)**

**Non-invasive measurement of liver steatosis by Controlled Attenuation Parameter (CAP) using FibroScan® in patients with Nonalcoholic Fatty Liver Disease (NAFLD)**

K. Enooku<sup>1</sup>, R. Tateishi<sup>2</sup>, N. Fujiwara<sup>2</sup>, S. Mikami<sup>2</sup>, T. Minami<sup>2</sup>, M. Sato<sup>2</sup>, K. Uchino<sup>2</sup>, Y. Kondo<sup>2</sup>, H. Yoshida<sup>2</sup>, H. Ikeda<sup>1</sup>, K. Koike<sup>2</sup>

*1) Department of Clinical Laboratory Medicine, The University of Tokyo, 2) Dpt of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Japan*

**Background/aim:** The aim of this study was to evaluate the performance of controlled attenuation parameter (CAP) for the assessment of steatosis grade in patients with nonalcoholic fatty liver disease (NAFLD).

**Methods:** We enrolled patients with chronic liver injury who met the following criteria: (1) those who visited the authors' hospital from March 2012 to November 2012, (2) diagnosed as having NAFLD by liver biopsy with a history of alcohol consumption  $< 20$ g/day, (3) underwent 10 valid liver stiffness measurements by Fibroscan. Blood sample, liver stiffness measurement, CAP assessment and liver biopsy were performed on each patient. The following parameters were also determined at the time of liver biopsy: weight, height, waist circumference, and alcohol consumption. Steatosis was categorized according to the NAFLD Activity Score (NAS) (S0,  $< 5\%$ ; S1, 5-33%; S2, 34-66%; and S3,  $> 66\%$ ) and assessed as the percentage of hepatocytes containing lipid droplets. The performance of CAP for

diagnosing steatosis as compared with biopsy was assessed using areas under receiver operating characteristic curves (AUROC).

**Results:** A total of 62 patients fulfilled the inclusion criteria. The majority (75.8%) was male and the median age was 60.9 years (IQR 43.5-69.5). The median BMI was 27.7 kg/m<sup>2</sup> (IQR 26.1-29.3). CAP was significantly correlated with sex, age, BMI, Platelet count, ALT, HDL cholesterol, triglycerides level, but not with GGT and AST levels. The median CAP values of patients with S0, S1, S2 and S3 were 226 (IQR 207-257.5), 285.0 (273-324), 335 (285-356.5), and 334 (316.2-340.5) dB/m respectively. Although CAP was not significantly different between patients with S2 and S3 steatosis (P = 0.60), differences between the remaining steatosis categories were significant (P < 0.05). The AUROCs of the CAP for ≥5%, >33% and >66% steatosis were 0.87, 0.81 and 0.75, respectively. With the optimal cut-off value of 270 dB/m for detecting ≥5% steatosis, CAP had 84.3% sensitivity, 81.8% specificity, and 95.6% positive and 52.9% negative predictive values.

**Conclusions:** CAP is a useful tool to assess steatosis of NAFLD patients non-invasively. Especially, CAP can detect steatosis at a level of ≥5% very efficiently.

**Poster CROI 2013 (March 3-6)**

**Inter-observer concordance in Controlled Attenuation Parameter Measurement, a novel tool for the assessment of hepatic steatosis**

Eva Recio<sup>1</sup>, K Neukam<sup>1</sup>, C Cifuentes<sup>1</sup>, M Mancebo<sup>1</sup>, J Macias<sup>1</sup>, C Almeida<sup>1</sup>, N Merchante<sup>1</sup>, J Mira<sup>1</sup>, A Rivero-Juarez<sup>2</sup>, and J Pineda<sup>1</sup>

1. Hosp Univ de Valme, Seville, Spain  
 2. Maimonides Inst for Biomed Res, Hosp Univ Reina Sofia, Cordoba, Spain

**Background:** The combination of transient elastometry (TE) with controlled attenuation parameter (CAP) allows non-invasive measurements of hepatic steatosis (HS) simultaneously to liver stiffness. TE is characterized by a high reproducibility and low inter-observational variability in hepatitis C virus (HCV)+patients with or without HIV co-infection. Nevertheless, no data are available on inter-observer differences in CAP values. This is a relevant point, since HS is a very common disorder among HIV+ patients, and accurate non-invasive diagnosis is critical. Accordingly, the objective of this study was to assess the concordance of CAP measurements between 2 independent observers in patients infected with HIV and/or hepatitis virus.

**Methods:** In a cross-sectional, prospective study conducted from December 2011 to March 2012 in a university hospital in Spain, CAP-enabled TE acquisitions were performed by 2 independent observers in 118 consecutive patients with HIV and/or hepatitis virus infection. The inter-observer concordance between the CAP value measurements was assessed using the intra-class correlation coefficient (ICC) and the concordance of the classification of patients regarding the grades of HS

was characterized using the kappa index. Patients with CAP ≥238 dB/m were considered to bear significant HS (≥10% hepatocytes involved), as previously reported.

**Results:** 78% of patients were male; 20 (17%) patients were HIV mono-infected, 44 (37.3%) HCV mono-infected, and 52 (44%) showed HIV/HCV co-infection. The median (Q1-Q3) values of CAP obtained by the first and the second observer were 228 (205-265) and 227 (196-269) dB/m, respectively. The median (interquartile range) of the absolute difference of CAP values between the 2 observers was 20 (10-41) dB/m. The overall ICC was 0.84 (95% confidence interval, 0.77-0.88). The kappa index for the concordance of classification for the presence of significant HS was 0.55. No factor was associated with a greater concordance between observers.

**Conclusions:** The concordance of CAP values obtained by 2 observers is good. Therefore, the determination of HS by means of CAP in HIV and/or hepatitis virus infection represents an observer-independent and easily performable method. However, the concordance of the diagnosis of significant HS, defined by the cutoff of 238 dB/m, is suboptimal.

**Poster CROI 2013 (March 3-6)**

**Prevalence and Factors Associated with Liver Steatosis Measured by Transient Elastography with Controlled Attenuation Parameter in HIV Infection**

Juan Macias<sup>1</sup>, J Gonzalez<sup>2</sup>, C Tural<sup>3</sup>, E Ortega<sup>4</sup>, F Pulido<sup>5</sup>, R Rubio<sup>5</sup>, C Cifuentes<sup>1</sup>, C de Alvaro<sup>6</sup>, A Burgos<sup>6</sup>, J Pineda<sup>1</sup>, and ESTAMPA Study Group

1. Hosp Univ de Valme, Seville, Spain  
 2. Hosp Univ La Paz, Madrid, Spain  
 3. Hosp Univ Germans Trias i Pujol, Badalona, Spain  
 4. Hosp Gen Univ de Valencia, Spain  
 5. Hosp Univ 12 de Octubre, Madrid, Spain  
 6. Abbott Labs, Madrid, Spain

**Background:** Fatty liver disease is one of the most important causes of liver disease. Among HIV+ individuals, data on hepatic steatosis (HS) and steatohepatitis mainly come from liver biopsy studies in HIV/hepatitis C virus (HCV) co-infection. Accurate non-invasive evaluation of HS is currently possible applying the Controlled Attenuation Parameter (CAP) with transient elastography (TE). This allows screening large and unselected HIV+ populations. Thus, we aimed at assessing the prevalence and factors associated with significant HS (SHS, HS involving ≥10% hepatocytes) in HIV+ patients.

**Methods:** 505 HIV+ patients were included in this cross-sectional prospective study. All patients underwent a TE with CAP. The previously identified CAP cut-off of 238 dB/m defined SHS. We analyzed the associations between SHS and gender, other demographics, metabolic data, co-infections and drug therapy.

**Results:** 346 (67%) were male. Median (relative inter-quartile range [RIQ]) age was 46 (41-49) years. Median (RIQ) CD4 cell count was 549 (355-739) cells/μL. Median (RIQ) CAP value was 226 (196-261) dB/m. Median (RIQ) body mass index (BMI) was 23.2 (20.9-26)



kg/m<sup>2</sup>. 254 (50%) patients were anti-HCV+, and 34 (6.7%) were hepatitis B surface antigen (HBsAg)+. SHS was detected in 201 (40%) patients. 149 (43%) men and 52 (33%) women showed SHS ( $p = 2.7 \times 10^{-2}$ ). Individuals with and without plasma HIV RNA  $\leq 50$  copies/mL presented SHS in 168 (42%) and 33 (31%) cases, respectively ( $p = 3 \times 10^{-2}$ ). Associations of metabolic factors with SHS are shown in the Table. SHS was observed in 102 (36%) patients exposed to protease inhibitor/ritonavir (PI/r) vs 97 (45%) not exposed to PI/r ( $p = 4.2 \times 10^{-2}$ ). Subjects with and without exposure to nevirapine (NVP) showed SHS in 49 (32%) vs 150 (43%) cases, respectively ( $p = 2.2 \times 10^{-2}$ ). The only factor independently associated with SHS was body mass index (BMI) (per unit increase, adjusted odds ratio [OR] [95% confidence interval] 1.33 [1.22-1.46];  $p < 10^{-6}$ ).

Variable	CAP < 238 dB/m <sup>+</sup> Mean (SD)	CAP ≥ 238 dB/m <sup>+</sup> Mean (SD)	p
BMI, kg/m <sup>2</sup>	22.4(3)	25.4(3.9)	<10 <sup>-6</sup>
Waist/hip ratio	0.92(0.07)	0.97(0.07)	<10 <sup>-6</sup>
Diastolic blood pressure, mmHg	75(10)	79(10)	1.04x10 <sup>-4</sup>
Fasting plasma glucose, mg/dL	93(19)	99(19)	2x10 <sup>-3</sup>
Triglycerides, mg/dL	135(106)	167(125)	2x10 <sup>-3</sup>
Total cholesterol, mg/dL	180(38)	187(39)	3.3x10 <sup>-2</sup>
HDL cholesterol, mg/dL	51(16)	48(16)	3.9x10 <sup>-2</sup>

**Conclusions:** SHS measured by CAP is highly prevalent among HIV+ patients. Overweight is the main predictor of HS. Other metabolic factors, also apparently associated with HS, are very likely to be confounders, because they are strongly dependent of overweight.

**Poster AASLD 2012 (November 9-13)**

**Controlled Attenuation Parameter (CAP) for the detection of hepatic steatosis in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD)**

S. Naveau<sup>1</sup>; G. Perlemuter<sup>1</sup>; M. Zioli<sup>4</sup>; D. Carmona<sup>3</sup>; J. Trinchet<sup>3</sup>; S. Prevot<sup>2</sup>; P. Nohra<sup>1</sup>; M. NakseuNguefang-Njike<sup>1</sup>; M. Beaugrand<sup>3</sup>

- 1. Gastroenterology Unit, Hôpital Antoine Bécélère, Clamart, France
- 2. Pathology Unit, Hôpital Antoine Bécélère, Clamart, France
- 3. Gastroenterology Unit, Hôpital Jean Verdier, Bondy, France
- 4. Pathology Unit, Hôpital Jean Verdier, Bondy, France

Steatosis may render the liver more vulnerable to injury when afflicted by other liver diseases. The CAP is a novel physical parameter based on the properties of ultrasonic signals acquired by the FibroScan<sup>®</sup> which was developed to assess liver steatosis.

**The aim** of this study was to assess diagnostic value of CAP in patients with ALD and NAFLD.

**Patients and Methods:** 186 patients who underwent liver biopsy and FibroScan<sup>®</sup> using regular probe within 30 days in two liver units were enrolled. 36 patients were excluded because of an invalidated FibroScan<sup>®</sup> examination. 150 patients with ALD (n=116) and NAFLD (n=36) (113 men, 37 women) mean age 52±0.8 years (mean±SE) and with body mass index (BMI) of 25.6±0.4 were included. These patients underwent

liver biopsy and FibroScan<sup>®</sup> using regular probe within 30 days in two liver units. Interval between liver biopsy and CAP measurement was 0.7±0.5 day. Steatosis was graded as S0: steatosis ≤5% (n=16), S1:6-10% (n=18), S2:11-33% (n=35), S3:34-66% (n=59), S4:>66% (n=22). Inflammation, ballooning degeneration and fibrosis were assessed according to the Kleiner-Brunt scores. Univariate analysis was performed using Spearman correlation and multivariate analysis was performed using multiple linear and multiple group logistic regression. Performance of CAP was assessed using the receiver operating characteristic (ROC) analysis and area under ROC curve (AUROC).

**Results:** Median CAP value was significantly higher in S3 and S4 patients than in S0 and S1 patients. In univariate analysis CAP was correlated with steatosis grade (r=0.50, p<0.0001), BMI (0.45, p<0.0001), NAFLD Activity Score (NAS) (r=0.32, p<0.0005), the ratio of the interquartile range (IQR) of CAP values to the median (IQR/Mcap) (r=0.62, p<0.0001) and the aetiology (r=0.28, p=0.001). After controlling for BMI, aetiology was no more significantly correlated with CAP (r=0.12, p=0.17). In multiple regressions (dependent variable: CAP) including NAS, BMI, steatosis grade, fibrosis stage, and IQR/Mcap, NAS was no more correlated with CAP. Finally in the multiple group logistic regression (dependent variable: steatosis grade) including CAP, BMI, NAS and IQR/Mcap, CAP (p<0.001) and NAS (p<0.001) were significantly correlated with steatosis grade after adjusting for all others terms. The AUROCs of the CAP for >5%, >10%, >33% and >66% steatosis were 0.76 (95%CI: 0.61-0.86; prevalence: 0.89), 0.79 (95%CI: 0.69-0.87; prevalence: 0.77), 0.78 (95%CI: 0.69-0.84; prevalence: 0.54), and 0.79 (95%CI: 0.66-0.89; prevalence: 0.15) respectively.

**Conclusion:** The CAP is promising tool for the non invasive detection of steatosis in patients with ALD and NAFLD.

**Poster EASL 2012 (April 18-22)**

**The performance of controlled attenuation parameter (CAP) for the non-invasive evaluation of steatosis using FibroScan<sup>®</sup>. Preliminary results**

M. Lupsor, R. Badea, H. Stefanescu, D. Feier, A. Tamas, Z. Sparchez

Ultrasonography, 3rd Medical Clinic, University of Medicine and Pharmacy, Cluj-Napoca, Romania.

**Background and objective:** Steatosis is a common histological finding in patient with chronic liver disease (CLD). Up to now liver biopsy (LB) was the gold standard to diagnose steatosis. Controlled Attenuation Parameter (CAP) is a novel non-invasive parameter measuring the attenuation of ultrasound generated by FibroScan<sup>®</sup>. We aim to assess diagnostic value of CAP in predicting steatosis in CLD. To our knowledge, this is the first independent validation study on the CAP vs liver biopsy.

**Patients and methods:** 71 CLD patients (14 with HBV, 54-HCV, 3-NAFLD), mean age 50.07years, 73.2% females, who underwent LB and FibroScan<sup>®</sup> (both CAP and liver



stiffness measurement) were enrolled. The mean number of portal spaces and the mean length of liver biopsy specimens were 13, and 15 mm respectively. Steatosis was assessed by a single expert pathologist, blinded to FibroScan® and clinical data as: S0:steatosis in less than 5% of hepatocytes, S1:6-32%, S2:33-100%. The diagnostic performance of CAP was assessed using sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV), positive (+LR) and negative (-LR) likelihood ratios and area under ROC curves (AUROC)

**Results:** There were 35 patients with S0, 26- S1 and 10- S2. The mean CAP value was 231.94±52.37 (201.50±35.85 in S0 patients, 247.96±44.33 in S1, respectively 293.80±48.60 in S2, p< 0.0001). CAP values were significantly different between steatosis grades (S0-S1: p< 0.0001, S1-S2: p=0.011, respectively S0-S2: p< 0.0001). Diagnostic performance of CAP to detect the different grades of steatosis is summarized in Table 1.

	S0vsS12	S01vsS2
CAP cutoff value	≥230	≥278
Se(%)	75	70
Sp(%)	85.29	90
+LR	5.10	7
-LR	0.29	0.33
PPV(%)	84.4	53.8
NPV(%)	76.3	94.7
AUROC	0.830	0.852

[Table 1]

**Conclusion:** CAP is a promising non-invasive tool to detect steatosis in CLD patients.

**Oral Presentation AIUM 2012 (March 29-Apr. 1<sup>st</sup>)**

**Controlled Attenuation Parameter (CAP): a novel FibroScan®-based tool to assess liver steatosis**

Magali Sasso, Laurent Sandrin, Véronique Miette

Echosens, R&D Department, 153 avenue d'Italie, 75013 Paris, France

**Objective:** Steatosis designates the accumulation of fat in liver cells. Its worldwide prevalence is very high (from 20 up to 95%). There is currently a need for non-invasive, screening friendly methods to detect steatosis. Fibroscan® is an ultrasound-based Vibration Control Transient Elastography (VCTETM) device used to diagnose liver fibrosis and cirrhosis by measuring the liver stiffness. A novel Controlled Attenuation Parameter (CAP) has been devised to target specifically liver steatosis using a sophisticated processed based on VCTETM. The objective of this work is to validate CAP as an estimate of ultrasound attenuation and validate its clinical performance in vivo.

**Method:** Validation on Field II simulations: Simulations were performed in the Fibroscan® configuration, in a homogeneous medium with attenuation varying from 100 dB.m<sup>-1</sup> to 350 dB.m<sup>-1</sup>. CAP was evaluated on each dataset and compared to reference value.

Validation on tissue-mimicking phantom: CAP was measured on a bi-layer CIRS ultrasound phantom and compared to the value given by the manufacturer.

In vivo validation: CAP was assessed in a cohort of 115 patients with liver diseases:

42 hepatitis C and 17 hepatitis B virus, 39 alcoholic and 17 non-alcoholic fatty liver disease. Steatosis was graded on liver biopsy as follows, S0: ≤10%, S1: 11~33%, S2: 33~66%, S3≥67% of hepatocyte with fat. Performance of the CAP was appraised using AUROC (Area Under the Receiver Operating Curve).

**Results:** Field II simulations: CAP values are in adequation with attenuation values set in Field II, the averaged RMSE is low: 2 dB.m<sup>-1</sup>. Tissue-mimicking phantom: CAP = 0.60 dB.cm<sup>-1</sup>.MHz<sup>-1</sup> in the 0.5±0.05 layer and 0.79 in the 0.7±0.07 layer. CAP is slight higher than values given by CIRS probably due to different experimental set-up and physical attenuation models. In vivo: CAP is excellent for the diagnosis of steatosis ≥S1: AUROC = 0.91 (Se=0.91, Sp=0.81) and ≥S2: AUROC = 0.95 (Se=0.89, Sp=0.86). Results were Jack-Knife cross-validated. CAP can also quantify steatosis by efficiently separating the steatosis grades.

**Conclusion:** A measure of ultrasound attenuation to assess steatosis has been developed on the Fibroscan®. CAP performs very well in detecting more than 10% steatosis and can be used for steatosis quantification.

**Poster APASL 2012 (Feb. 16-19)**

**Hepatology perisinusoidal fibrosis is associated with transient elastography (TE) and Controlled Attenuation Parameter (CAP) values measured by FibroScan®**

Ana Carolina Cardoso<sup>1</sup>, Magali C. Sasso<sup>2</sup>, Celine Fournier<sup>3</sup>, Michel Beaugrand<sup>4</sup>, Catherine Douvin<sup>5</sup>, Victor de Ledinghen<sup>6</sup>, Raoul Poupon<sup>7</sup>, Marianne Ziol<sup>8</sup>, Pierre Bedossa<sup>9</sup>, Patrick Marcellin<sup>10</sup>

- 1) Beaujon Hospital - Paris 7 Diderot University, Clichy, France;
- 2) R&D Dept., Echosens, Paris, France,
- 3) Medical Affairs Dept., Echosens, Paris, France,
- 4) Jean Verdier Hospital, Bondy, France,
- 5) Henri Mondor Hospital,
- 6) Haut Leveque Hospital, Pessac, France;
- 7) Saint-Antoine Hospital, Paris, France;
- 8) Jean Verdier Hospital, Bondy, France.;
- 9) Beaujon Hospital -Paris 7 Diderot University, Clichy, France;
- 10) Beaujon Hospital -Paris 7 Diderot University, Clichy, France.

**Background:** Perisinusoidal fibrosis (PF) may be related to many causes, including metabolic disorders. Steatosis may be associated with the progression of liver fibrosis but its evaluation by non invasive methods remains a challenge. Controlled Attenuation Parameter (CAP) evaluating liver steatosis based on FibroScan.

**Methods:** 136 CHB patients were prospectively included (63% men, age = 38y~3y). All patients underwent within 60 days both liver biopsy (LB) and FibroScan

**Results:** CAP was only associated to steatosis (p\10-6). PF was mild/ absent in 45%, moderate in 39% and marked in 16% of patients. In univariate analysis, PF was correlated with TE (p\10-4) and CAP (p\10-3), with fibrosis (p=0.002) and activity (p\10-5), at the limit of

significance for steatosis and NASH (p=0.06) and not with metabolic syndrome and HBV-DNA levels. In multivariate analysis PF was associated with TE and CAP, activity and steatosis.

**Conclusions:** CAP is an accurate tool to detect and quantify steatosis in CHB patients. Moderate to marked PF was observed in 55% of our CHB patients. PF is independently associated with TE and CAP measurements.

**Poster AASLD 2011 (Nov. 4-8)**

**Steatosis assessment by CAP™ in patients with alcoholic and non-alcoholic fatty liver disease**

M. Beaugrand<sup>1</sup>; D. Carmona<sup>1</sup>; M. Ziol<sup>2</sup>; G. Perlemuter<sup>3</sup>; S. Naveau<sup>3</sup>; S. Prevot<sup>4</sup>; C. Fournier<sup>5</sup>; L. Sandrin<sup>5</sup>; V. Miette<sup>5</sup>; M. Sasso<sup>5</sup>

- 1. Liver Unit, Jean Verdier Hospital, Bondy, France
- 2. Pathology, Jean Verdier Hospital, Bondy, France
- 3. Liver Unit, Antoine Béclère Hospital, Clamart, France
- 4. Pathology, Antoine Béclère Hospital, Clamart, France
- 5. R&D, Echosens, Paris, France

**Background and Objective:** Steatosis is a common histological finding in patient with alcoholic and non alcoholic fatty liver disease (ALD & NAFLD). Up to now liver biopsy (LB) is the gold standard to diagnose steatosis, ultrasonography being poorly sensitive and reproducible. Controlled Attenuation Parameter (CAP) is a novel non-invasive parameter measuring the attenuation of ultrasound generated by Fibroscan®. The aim of this study was to assess diagnostic value of CAP in ALD and NAFLD patients.

**Patients & Methods:** 130 patients with ALD (n=101) and NAFLD (n=29) who underwent both LB and FibroScan® (both CAP and liver stiffness measurement using regular or M probe) within 30 days in two liver units were enrolled (72% from center 1). Steatosis was assessed by two expert pathologists, blinded to FibroScan® and clinical data. Steatosis was graded as: S0: steatosis in less than 6% of hepatocytes, S1: 6-10%, S2: 11-33%, S3: 34-66%, S4: 67-100%. Inflammation, ballooning degeneration & fibrosis were assessed according to the Kleiner-Brunt scores. Univariate analysis was performed using Kendall rank correlation, multivariate analysis was performed using multiple linear or logistic regression. Performance of CAP was assessed using the receiver operating characteristic (ROC) analysis and area under ROC curve (AUROC).

**Results:** 19 patients were S0, 13 were S1, 24 were S2, 49 were S3 and 25 were S4. In univariate analysis, CAP is related to steatosis ( $\tau=0.43$ ,  $p<10^{-10}$ ), inflammation ( $\tau=0.18$ ,  $p=0.01$ ), ballooning degeneration ( $\tau=0.18$ ,  $p=0.01$ ), etiology ( $\tau=-0.20$ ,  $p=0.004$ ) but CAP is independent to fibrosis stage. In multivariate analysis, CAP is only related to steatosis ( $p<10^{-11}$ ). Diagnostic performance of CAP to detect the different stage of steatosis is summarized in Table 1. Performance is good for the detection of steatosis from 6%. However, performance is poor for the detection of steatosis  $\geq 67\%$ . Most of misclassified patients for steatosis  $\geq 67\%$  were false positives which are significantly related in both uni

and multivariate analysis to the length of LB and IQR of CAP, emphasizing the heterogeneous distribution of steatosis as well as the risk of sampling error of LB.

**Conclusion:** CAP is a promising non-invasive tool to detect steatosis from 6% in ALD and NAFLD patients.

**Table 1. Performance of CAP™ for the detection of steatosis**

	S0 vs S1234 (S $\geq$ 6%)	S01 vs S234 (S $\geq$ 11%)	S012 vs S34 (S $\geq$ 34%)	S0123 vs S4 ( $\geq$ 67%)
AUROC (95% CI)	0.81 (0.70-0.92)	0.85 (0.77-0.93)	0.84 (0.77-0.91)	0.69 (0.59-0.79)
	n <sub>S1234</sub> =85%	n <sub>S234</sub> =75%	n <sub>S34</sub> =57%	n <sub>S4</sub> =19%

**Oral Presentation EASL 2011 (March 30-April 3<sup>rd</sup>)**

**Non Invasive diagnosis of steatosis using CAP by FibroScan®. A prospective study**

V. de Ledinghen<sup>1,2\*</sup>, B. Le Bail<sup>3</sup>, J. Vergniol<sup>4</sup>, J. Foucher<sup>1</sup>, W. Merrouche<sup>1</sup>, C. Fournier<sup>5</sup>, L. Sandrin<sup>5</sup>, V. Miette<sup>5</sup>, M. Sasso<sup>5</sup>

- 1) CHU Bordeaux, Pessac
- 2) INSERM U889, Université Bordeaux 2
- 3) CHU Bordeaux, Bordeaux
- 4) CHU Besançon, Pessac
- 5) Echosens, Paris, France. \*victor.deledinghen@chu-bordeaux.fr

**Introduction:** Recently, a retrospective study showed that CAP (Controlled Attenuation Parameter), based on FibroScan® principle, could efficiently separate several steatosis grades (1). The aim of this study was to prospectively evaluate the performance of CAP for the diagnosis of steatosis in patients with chronic liver disease and to compare it with another non-invasive method (steatotest).

**Patients and methods:** From June 2009 to June 2010, consecutive patients with chronic liver disease had steatosis diagnosis using CAP, blood sample for steatotest and liver biopsy the same day. All liver biopsies were analysed by one expert anatomopathologist. Fibrosis was assessed using Metavir or Brunt score depending on the aetiology. Steatosis was quantified as follow: S0 $\leq$ 10%, S1: 11~33%, S2: 34~66%, S3~67%. Correlation was assessed using Spearman coefficient. Performance of CAP was appraised using ROC curves.

**Results:** Characteristic of the 112 patients included were: 49% male, age 55 years, BMI 25 kg/m<sup>2</sup>, HCV 36%, HBV 5%, NAFLD/ALD 15%. Steatosis repartition was: S0 53%, S1 18%, S2 14%, S3 15%. Fibrosis staging was F0F1 54%, F2 18%, F3 21%, F4 7%. CAP was significantly correlated to steatosis grade ( $r=0.49$   $p<0.0001$ ), fibrosis ( $r=0.16$ ,  $p=0.02$ ) but not to liver stiffness. In bivariate analysis including steatosis grade and fibrosis, stage CAP was only related to steatosis (OR = 4.26 05%CI 3.14-5.78). AUROCS for the diagnosis of steatosis are indicated in the table.

	S>0	S>1	S>2
CAP	0.82 (0.74-0.90)	0.86 (0.78-0.95)	0.92 (0.83-1.0)
Steato Test	0.68 (0.58-0.78)	0.72 (0.61-0.83)	0.76 (0.62-0.90)

[AUROCs for the diagnosis of steatosis]

With Youden index, performances of CAP were: S>0 cutoff 233 dB/m, sensitivity 0.85, specificity 0.68, positive predictive value 0.70, negative predictive value 0.83 ; S>1 cutoff 266 dB/m, sensitivity 0.85, specificity 0.76, positive predictive value 0.60, negative predictive value 0.92; S>2 cutoff 318 dB/m, sensitivity 0.82, specificity 0.89, positive predictive value 0.58, negative predictive value 0.97.

**Conclusion:** CAP is very efficient to detect even minimal steatosis (10%). CAP being implemented on FibroScan®, both steatosis and fibrosis can be evaluated simultaneously, enlarging the spectrum of non invasive techniques for chronic liver disease management.

**Poster APASL 2011 (Feb. 17-20)**

**Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis in chronic hepatitis B**

Ana Carolina F. Cardoso<sup>1</sup>, Magali C. Sasso<sup>2</sup>, Véronique Miette<sup>2</sup>, Céline Fournier<sup>3</sup>, Laurent Sandrin<sup>2</sup>, Michel Beaugrand<sup>4</sup>, Catherine Douvin<sup>5</sup>, Victor de Ledinghen<sup>6</sup>, Raoul Poupon<sup>7</sup>, Marianne Ziol<sup>8</sup>, Pierre Bedossa<sup>9</sup>, Patrick Marcellin<sup>1</sup>

- 1. Hepatology, Beaujon Hospital - University Paris-Diderot, Clichy, France
- 2. R&D, Echosens, Paris, France
- 3. Medical Affairs, Echosens, Paris, France
- 4. Hepatology, Jean Verdier Hospital, Bondy, France
- 5. Hepatology, Henri Mondor Hospital, Créteil, France
- 6. Hepatology, Haut Lévêque Hospital, Pessac, France
- 7. Hepatology, Saint Antoine Hospital, Paris, France
- 8. Pathology, Jean Verdier Hospital, Bondy, France
- 9. Pathology, Beaujon Hospital-University Paris-Diderot, Clichy, France

**Background and Aims:** Steatosis may contribute to the progression of liver fibrosis in patients with chronic hepatitis B (CHB) but its evaluation by non invasive means is still a challenge. Since fat affects ultrasound propagation, a novel Controlled Attenuation Parameter (CAP) evaluated on the signals acquired by the FibroScan® has been developed. The aim of this work was to validate the CAP performance for detection and quantification of steatosis in CHB patients.

**Methods:** 133 consecutive CHB patients were prospectively included (62% men, age = 39±13 years). All patients underwent both liver biopsy (LB) and FibroScan® in 5 liver units within 60 days. The CAP was retrospectively evaluated on the raw data acquired by the FibroScan® and corresponds to the ultrasonic attenuation value in dB/m at the centre frequency of the probe (3.5 MHz). LBs were analysed by the same pathologist. Activity and fibrosis were staged according to the METAVIR classification. Steatosis was graded according to the following scale: S0: steatosis ≤10% of hepatocytes, S1: 11~33%, S2: 34~66%, S3: ≥67%. Proportions in each steatosis grade were: 77%, 11%, 9% and 3%, respectively. Performance was evaluated in terms of Area Under the Receiver Operating Characteristic (AUROC).

**Results:** In univariate analysis, liver stiffness (LS) was significantly (p<0.05) correlated to fibrosis (Spearman ρ=0.60), gender, activity, steatosis, age and sinusoidal fibrosis. By multivariate analysis, liver stiffness was associated only with liver fibrosis (OR=19.9 [6.65-59.8]). In univariate analysis, CAP was mainly correlated with

steatosis (p=0.50, p<107) but also with BMI, presence of NASH and liver fibrosis. In multivariate analysis CAP was associated only with steatosis (OR=7e13 [4e8-1e19]). Performances in terms of AUROC (i) for LS were: 0.80 (0.72-0.89) for F≥2, 0.91 (0.84-0.99) for F≥3 and 0.91 (0.78-1.00) for F=4; (ii) for CAP: 0.82 (0.74-0.89) for S≥10% and 0.81 (0.72-0.90) for S≥30%. Similar results were obtained for both LS and CAP using jack-knife cross validation.

**Conclusion:** The CAP is an accurate new non invasive tool to detect and quantify steatosis in CHB patients.

**Oral Presentation APASL 2011 (Feb. 17-20)**

**Non invasive diagnosis of steatosis using CAP by FibroScan®**

Victor de Ledinghen<sup>1</sup>, Brigitte le Bail<sup>2</sup>, Julien Vergniol<sup>1</sup>, Juliette Foucher<sup>1</sup>, Wassil Merrouche<sup>1</sup>, Céline Fournier<sup>3</sup>, Laurent Sandrin<sup>4</sup>, Véronique Miette<sup>4</sup>, Magali Sasso<sup>4</sup>

- 1) Hepatology, Hôpital Haut Lévêque, Pessac, France
- 2) Pathology, Hôpital Pellegrin, Bordeaux, France
- 3) Medical Affairs, Echosens, Paris, France
- 4) R&D Department, Echosens, Paris, France

**Introduction:** Recently, a retrospective study showed that CAP (Controlled Attenuation Parameter), based on Fibroscan® principle, could efficiently separate several steatosis grades (1). The aim of this study was to prospectively evaluate the performance of CAP for the diagnosis of steatosis in patients with chronic liver disease and to compare it with another non-invasive method (steatotest).

**Patients and methods:** From June 2009 to June 2010, consecutive patients with chronic liver disease had steatosis diagnosis using CAP (with M probe of FibroScan®), blood sample for steatotest and liver biopsy the same day. All liver biopsies were analysed by one expert anatomopathologist. Fibrosis was assessed using METAVIR or Brunt score depending on the aetiology. Steatosis was quantified as the percentage of hepatocyte with fat: S0≤10%, S1: 11~33%, S2: 34~66%, S3≥67%. Correlation was assessed using Spearman coefficient. Performance of CAP was appraised using Receiver Operating Characteristics.

**Results:** Characteristic of the 112 patients included were as follow: 49% male, age 55 years, BMI 25 kg/m<sup>2</sup>, HCV 36%, HBV 5%, NAFLD/ALD 15%. Steatosis repartition was: S0 53%, S1 18%, S2 14%, S3 15%. Fibrosis staging was F0F1 54%, F2 18%, F3 21%, F4 7%. CAP was significantly correlated to steatosis grade (r=0.49 p<0.0001), fibrosis (r=0.16, p=0.02) but not to liver stiffness. In bivariate analysis including steatosis grade and fibrosis stage, CAP was only related to steatosis (OR = 4.26 05%CI 3.14-5.78). AUROCS for the diagnosis of steatosis are indicated in the table.

	S>0	S>1	S>2
CAP	0.82 (0.74-0.90)	0.86 (0.78-0.95)	0.92 (0.83-1.0)
Steatotest	0.68 (0.58-0.78)	0.72 (0.61-0.83)	0.76 (0.62-0.90)

With Youden index, performances of CAP were:  $S \geq 1$  cutoff 233 dB/m, sensitivity 0.85, specificity 0.68, positive predictive value 0.70, negative predictive value 0.83;  $S \geq 2$  cutoff 266 dB/m, sensitivity 0.85, specificity 0.76, positive predictive value 0.60, negative predictive value 0.92;  $S \geq 3$  cutoff 318 dB/m, sensitivity 0.82, specificity 0.89, positive predictive value 0.58, negative predictive value 0.97.

**Conclusion.** CAP is very efficient to detect even minimal steatosis (10%). CAP being implemented on FibroScan®, both steatosis and fibrosis can be evaluated simultaneously, enlarging the spectrum of non invasive techniques for chronic liver disease management.

(1) Sasso et al. UMB2010;36:1825-35.

**Oral Presentation AASLD 2010 (Oct. 29-Nov. 2<sup>nd</sup>)**

**Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis in chronic hepatitis B.**

A.C. Cardoso<sup>1</sup>, M. Sasso<sup>2</sup>, V. Miette<sup>2</sup>, C. Fournier<sup>3</sup>, L. Sandrin<sup>2</sup>, M. Beaugrand<sup>4</sup>, C. Douvin<sup>5</sup>, V. de Ledinghen<sup>6</sup>, R. Poupon<sup>7</sup>, M. Ziol<sup>8</sup>, P. Bedossa<sup>9</sup>, P. Marcellin<sup>1</sup>

- 1) Hepatology unit - Hôpital Beaujon, Université Denis Diderot-Paris7, Clichy, France
- 2) R&D Department, Echosens, Paris, France
- 3) Medical Affairs Department, Echosens, Paris, France
- 4) Hepatology unit - Hôpital Jean Verdier, Bondy
- 5) Hepatology unit - Hôpital Henri Mondor, Créteil
- 6) Hepatology unit - Hôpital Haut-Lévêque, Pessac
- 7) Hepatology unit - Hôpital Saint-Antoine, Paris
- 8) Pathology unit - Hôpital Jean Verdier, Bondy
- 9) Pathology unit - Hôpital Beaujon, Université Denis Diderot-Paris7, Clichy, France

**Background and Aims:** Steatosis may contribute to the progression of liver fibrosis in patients with chronic hepatitis B (CHB) but its evaluation by non invasive means is still a challenge. Since fat affects ultrasound propagation, a novel Controlled Attenuation Parameter (CAP) evaluated on the signals acquired by the FibroScan® has been developed. The aim of this work was to validate the CAP performance for detection and quantification of steatosis in CHB patients.

**Methods:** 133 consecutive CHB patients were prospectively included (62% men, age = 39±13 years). All patients underwent both liver biopsy (LB) and FibroScan® in 5 liver units within 60 days. The CAP was retrospectively evaluated on the raw data acquired by the FibroScan® and corresponds to the ultrasonic attenuation value in dB/m at the centre frequency of the probe (3.5 MHz). LBs were analysed by the same pathologist. Activity and fibrosis were staged according to the METAVIR classification. Steatosis was graded according to the following scale: S0: steatosis ≤10% of hepatocytes, S1: 11~33%, S2: 34~66%, S3: ≥67%. Proportions in each steatosis grade were: 77%, 11%, 9% and 3%, respectively. Performance was evaluated in terms of Area Under the Receiver Operating Characteristic (AUROC).

**Results:** In univariate analysis, liver stiffness (LS) was significantly ( $p < 0.05$ ) correlated to fibrosis (Spearman  $\rho = 0.60$ ), gender, activity, steatosis, age and sinusoidal fibrosis. By multivariate analysis, liver stiffness was associated only with liver fibrosis (OR=19.9 [6.65-59.8]).

In univariate analysis, CAP was mainly correlated with steatosis ( $p = 0.50$ ,  $p < 10^{-7}$ ) but also with BMI, presence of NASH and liver fibrosis. In multivariate analysis CAP was associated only with steatosis (OR=7e13 [4e8-1e19]). Performances in terms of AUROC (i) for LS were: 0.80 (0.72-0.89) for  $F \geq 2$ , 0.91 (0.84-0.99) for  $F \geq 3$  and 0.91 (0.78-1.00) for  $F = 4$ ; (ii) for CAP: 0.82 (0.74-0.89) for  $S \geq 10\%$  and 0.81 (0.72-0.90) for  $S \geq 30\%$ . Similar results were obtained for both LS and CAP using jack-knife cross validation.

**Conclusion:** The CAP is an accurate new non invasive tool to detect and quantify steatosis in CHB patients.

**Poster AASLD 2010 (Oct. 29-Nov. 2<sup>nd</sup>)**

**CAP: a VCTE™-guided tool for hepatic steatosis detection – Preliminary results of a multicenter study in overweight and obese patients with chronic liver disease**

Magali C. Sasso<sup>1</sup>, Robert P. Myers<sup>2</sup>, Magdy Elkashab<sup>3</sup>, Gilles Pomier-Layrargues<sup>4</sup>, Andres Duarte-Rojo<sup>5</sup>, David K. Wong<sup>5</sup>, Melanie D. Beaton<sup>6</sup>, Mark A. Levstik<sup>6</sup>, Richard Kirsch<sup>7</sup>, Aaron Pollett<sup>7</sup>, Laurent Sandrin<sup>1</sup>, Veronique Miette<sup>1</sup>

- 1. R&D, Echosens, Paris, France.
- 2. Liver Unit, Division of gastroenterology, University of Calgary, Calgary, AB, Canada.
- 3. The Liver Center, Toronto, ON, Canada.
- 4. Liver Unit, Centre Hospitalier de l'Université de Montreal, Montreal, QC, Canada.
- 5. Toronto Western Hospital Liver Center, University of Toronto, Toronto, ON, Canada.
- 6. Multi-Organ Transplant Unit, University of Western Hospital, London, ON, Canada.
- 7. Department of Pathology, Mount Sinai Hospital, Toronto, ON, Canada.

**Objective:** Hepatic steatosis is a condition affecting 15~30% of the general population and up to 70% of the obese, that may accelerate fibrosis progression. There is a need for accurate, screening-friendly methods to detect steatosis. A novel Controlled Attenuation Parameter (CAP) guided by Vibration Control Transient Elastography has been devised to specifically target liver steatosis. The objective of this study was to validate the CAP for the detection of pathological steatosis in overweight and obese patients with chronic liver disease.

**Methods:** Between 07/2009 and 02/2010, 89 consecutive patients with BMI ≥ 28 kg.m<sup>-2</sup> who underwent liver biopsy (LB) and Fibroscan (FS) in 5 liver units were enrolled. 18 patients were excluded (LB unsuitable for interpretation or invalid FS). FS was performed using its 3.5MHz M probe. CAP was assessed on signals acquired by the FS. Steatosis was graded on LB as the percentage of hepatocytes with fatty accumulation by 2 experienced pathologists blinded to clinical data and CAP. In cases of disagreement, a consensus was reached. Patients were categorized into two groups: S0, no or insignificant steatosis (<10% of hepatocytes, 30% of the cohort) and S1, significant steatosis (≥10% hepatocytes, 70% of the cohort). Performance of CAP for detecting pathological steatosis (S1) was assessed using the area under the receiver operating characteristic (AUROC).

**Results:** 71 patients met the inclusion criteria (66% male; median age: 50 years [IQR 43~56]; median BMI: 32 kg.m<sup>-2</sup> [IQR 30~34]). 56% of the patients had NAFLD,



35% HCV, 10% HBV. CAP was significantly correlated with steatosis in percentage (Spearman  $\rho=0.55$ ;  $p<10^{-6}$ ) and grade ( $\rho=0.79$ ;  $p<10^{-16}$ ). Median CAP was significantly greater in S1 (321 dB/m [IQR 291-349]) than in S0 patients (253 dB/m [IQR 224-276]) ( $p<10^{-16}$ ). AUROC of the CAP for the detection of S1 vs. S0 was 0.85 (95%CI 0.76-0.94). At a cut-off of 291 dB/m (maximum Youden index), the CAP had a specificity = 0.86; sensitivity = 0.76; positive predictive value = 0.93; negative predictive value = 0.60. Similar results were obtained using the Jack-Knife cross-validation.

**Conclusion:** These preliminary results demonstrate satisfactory performance of the CAP. Although additional validation is pending from this ongoing study (target enrolment, 300 patients), these promising results support use of the CAP as a non-invasive, immediate and screening-friendly method to detect steatosis. Hence, the FS can provide two physical parameters - liver stiffness and CAP - related to fibrosis and steatosis, respectively; thereby enhancing the spectrum of non-invasive methods for the management of patients with liver disease.

**Oral Presentation I.E.E.E. 2010 (Oct. 1-14)**

**Controlled Attenuation Parameter (CAP): a novel VCTE™-guided tool to detect and quantify steatosis. principle and validation on field II simulations, tissue mimicking phantoms and clinically on patients with chronic liver disease**

Magali Sasso, Laurent Sandrin, Véronique Miette

R & D, Echosens, Paris, France

**Background, Motivation and Objective:** Steatosis designates the accumulation of fat in liver cells. Its worldwide prevalence is very high (from 20 up to 95%). There is currently a need for non-invasive, screening friendly methods to detect steatosis. FibroScan® is an ultrasound-based Vibration Control Transient Elastography (VCTE) device used to diagnose liver fibrosis and cirrhosis by measuring the liver stiffness. A novel Controlled Attenuation Parameter (CAP) has been devised to target specifically liver steatosis using a sophisticated process based on VCTE. The objective of this work is to describe the CAP principle, to validate the CAP as an estimate of ultrasonic attenuation and to assess its clinical performance.

**Statement of Contribution/Methods:** CAP measures the ultrasound attenuation in dB/m, at the centre frequency of the FibroScan® regular probe. Validation on simulations: Field II simulations were performed in the FibroScan® configuration (7 mm diameter piston, 3.5 MHz

sinusoidal excitation). Tissue scatterers were modeled as a 3D spatial distribution of independent points. Their numbers was set so as to reach the maximal speckle-to-noise ratio of 1.91 dB. Simulations were run in homogeneous media with attenuation varying from 100 to 350 dB/m. CAP was evaluated on each dataset and

compared to the reference value. Validation on tissue-mimicking phantom: CAP was measured on a bi-layer CIRS ultrasound phantom and compared to the value given by the manufacturer. Clinical validation: CAP was assessed in a cohort of 115 patients with liver diseases from various causes: 42 hepatitis C and 17 hepatitis B virus, 39 alcoholic and 17 non-alcoholic fatty liver disease. Steatosis was graded on liver biopsy as follows, S0:  $\leq 10\%$ , S1: 11~33%, S2: 33~66%, S3 $\geq 67\%$  of hepatocytes with fatty accumulation. Performance of the CAP was appraised using AUROC (Area Under the Receiver Operating Curve).

**Results:** Field II simulations: CAP was successively equal to 97.1 dB/m (to be compared to 100 set in Field II), 123 (/125), 149 (/150), 175 (/175), 201 (/200), 226 (/225), 252 (/250), 278 (/275), 303 (/300), 326 (/325), 348 (/350). The averaged RMSE is low: 2 dB/m. Tissue-mimicking phantom: CAP = 0.60 dB/cm/MHz in the  $0.5\pm 0.05$  layer and 0.79 in the  $0.7\pm 0.07$  layer. CAP is slightly higher than maximal values given by CIRS which can be explained by different experimental set-up and physical attenuation models. Clinical: CAP is excellent for the diagnosis of steatosis  $\geq S1$ : AUROC = 0.91 (Se=0.91, Sp=0.81) and  $\geq S2$ : AUROC = 0.95 (Se=0.89, Sp=0.86). Similar results were obtained on Jack-Knife cross validation. CAP can also quantify steatosis by efficiently separating the steatosis grades.

**Discussion and Conclusions:** A novel physical parameter based on VCTE has been developed on the FibroScan®. CAP was validated as an estimate of ultrasonic attenuation. CAP performs very well in detecting more than 10% steatosis and can be used for steatosis quantification.

**Oral Presentation ICO 2010 (July 11-15)**

**A novel non-invasive FibroScan®-based tool for the detection of hepatic steatosis in overweight and obese patients**

V. de Ledinghen<sup>3</sup>, M. Beaugrand<sup>1</sup>, M. Ziol<sup>2</sup>, C. Douvin<sup>4</sup>, C. Fournier<sup>5</sup>, L. Sandrin<sup>5</sup>, V. Miette<sup>5</sup>, M. Sasso<sup>5</sup>

1) Hepatology, Hôpital Jean Verdier, Bondy, France

2) Pathology, Hôpital Jean Verdier, Bondy, France

3) Hepatology, Hôpital Haut Lévéque, Bordeaux, France

4) Hepatology, Hôpital Henri Mondor, Créteil, France

5) Echosens, Paris, France

**Introduction:** Steatosis designates the intracellular accumulation of fat in the liver. Its prevalence is around 70% obese and 90% in severely obese patients. In obese patients steatosis is often associated with inflammation and fibrosis (Steato-Hepatitis, SH) which may silently progress until cirrhosis. The gold standard for fibrosis and steatosis assessment is Liver Biopsy (LB). Non invasive methods are needed differentiate steatosis from SH in obese patients. The FibroScan® is Vibration Control Transient Elastography device used to non-invasively assess liver fibrosis. A novel Controlled Attenuation Parameter (CAP) has been developed to diagnose



steatosis. The aim of this work is to validate the CAP in patients suffering from SH.

**Methods:** 61 overweight and obese patients (25≤BMI≥40) with SH who underwent LB were included. Steatosis was graded by the same pathologist as: S0: steatosis in less than 11% of hepatocytes, S1: 11~33%, S2: 34~100%. Repartition of patients in each grade was 20%, 25%, 56%, respectively.

**Results:** CAP was correlated to the steatosis (ρ=0.59, p<10<sup>-6</sup>). Its performance evaluated in terms of AUROC is summarized the Table.

	S0vsS1S2	S0S1vsS2
AUROC* (95% CI)	0.82 (0.70~0.93)	0.84 (0.74~0.94)

Area under Receiver Operating Curve

Table

**Conclusion:** The novel CAP can be used to detect steatosis in overweight and obese patients. Furthermore, its performance is good for the diagnosis of severe fibrosis and excellent for cirrhosis (data not shown). Clinical validation in a large cohort of obese patient is ongoing. Combination of both fibrosis and steatosis detection using the FibroScan® might differentiate simple steatosis from SH in obese patients.

**Poster EASL 2010 (April 14-18)**

**Controlled Attenuation Parameter: a novel FibroScan®-based tool to detect and quantify steatosis. preliminary study in patient with alcoholic and nonalcoholic fatty liver disease**

M. Beaugrand<sup>1\*</sup>, M. Zioli<sup>2</sup>, V. de Ledinghen<sup>3</sup>, C. Douvin<sup>4</sup>, C. Fournier<sup>5</sup>, L. Sandrin<sup>6</sup>, V. Miette<sup>6</sup>, M. Sasso<sup>6</sup>

- 1) Hepatology unit - Hôpital Jean Verdier
- 2) Pathology unit - Hôpital Jean Verdier, Bondy
- 3) Hepatology unit - Hôpital Haut-Lévêque, Pessac
- 4) Hepatology unit - Hôpital Henri Mondor, Créteil
- 5) Medical Affairs department, Echosens, Paris, France
- 6) R & D department, Echosens, Paris, France

**Background and Aims:** Steatosis may contribute to the progression of liver fibrosis especially in patients with Alcoholic and Non Alcoholic Fatty Liver Disease (ALD & NAFLD) but its evaluation by non invasive means is still a challenge. Since fat affects ultrasound propagation a novel Controlled Attenuation Parameter (CAP) evaluated on the signals acquired by the FibroScan® has been developed. The aim of this work is to validate the CAP performance for detection and quantification of steatosis in ALD and NAFLD patients.

**Methods:** 97 consecutive patients (66 ALD and 31 NAFLD) were prospectively included (74% men, age = 52±9 years). All patients underwent both liver biopsy (LB) and FibroScan® in 3 liver units within 7 days. The CAP was retrospectively evaluated on the raw data acquired by the FibroScan® and corresponds to the ultrasonic attenuation value in dB/m at the centre frequency of the probe (3.5 MHz). LB were analysed by the same pathologist. Fibrosis was staged according to the Brunt classification (FOF1: 22%, F2: 25%, F3: 20%, F4: 34%). Steatosis was graded according to the following scale: S0:

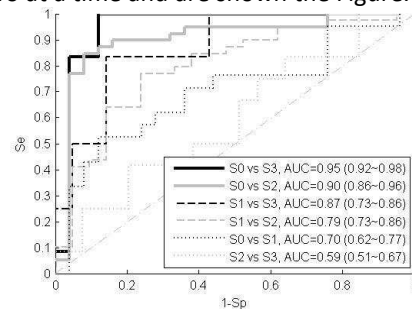
steatosis ≤10% of hepatocytes, S1: 11~33%, S2: 34~66%, S3: ≥67%. Prevalence in each steatosis grade was: 33%, 19%, 36% and 11%, respectively. Performance was evaluated in terms of Area Under the Receiver Operating Characteristic (AUROC).

**Results:** The CAP was correlated to steatosis (Spearman r=0.65, p< 10<sup>-12</sup>). Performance in terms of AUROC is summarized in the Table together with the Jack-Knife cross-validation performance.

AUROC (95% CI)	S0 vs S1S2S3 (≥11%)	S0S1 vs S2S3 (≥33%)	S0S1S2 vs S3 (≥67%)
CAP apparent performance	0.85 (0.77~0.93)	0.87 (0.79~0.94)	0.77 (0.60~0.93)
CAP Jack-Knife cross-validation performance	0.85 (0.76~0.94)	0.87 (0.79~0.94)	0.77 (0.65~0.89)

[Table]

ROC curves were also appraised between each grade, two at a time and are shown the Figure.



The CAP could effectively separate S0 from S1S2S3; S0S1 from S2S3; S0 from S2 and S3; S1 from S3 patients.

**Conclusion:** The CAP can be used to quantify steatosis in ALD and NAFLD patients. Performance is particularly satisfactory for the differentiation of S0 or S1 patients versus S2 or S3.

**Oral Presentation EASL 2010 (April 14-18)**

**Validation of Controlled Attenuation Parameter (CAP) as a non-invasive marker of steatosis in 228 patients with chronic liver disease from various causes**

M. Beaugrand<sup>1</sup>, V. de Ledinghen<sup>2</sup>, C. Douvin<sup>3</sup>, P. Marcellin<sup>4</sup>, R. Poupon<sup>5</sup>, C. Fournier<sup>6</sup>, L. Sandrin<sup>7</sup>, V. Miette<sup>7</sup>, M. Sasso<sup>7</sup>

- 1) Hepatology unit - Hôpital Jean Verdier, Bondy
- 2) Hepatology unit - Hôpital Haut-Lévêque, Pessac
- 3) Hepatology unit - Hôpital Henri Mondor, Créteil
- 4) Hepatology unit - Hôpital Beaujon, Clichy
- 5) Hepatology unit - Hôpital Saint-Antoine
- 6) Medical Affairs department, Echosens, Paris
- 7) R & D department, Echosens, Paris

**Background and Aims:** A novel Controlled Attenuation Parameter (CAP) using the signals recorded by the FibroScan®, corresponding to the ultrasonic attenuation inside the liver, has been devised. We previously established in a cohort of HCV patients that this parameter was not influenced by fibrosis but is closely related to the steatosis grade. The aim of this work is to validate the CAP performance in a population of patients with chronic liver disease from various causes, referred to Liver Biopsy (LB) in 5 liver units.

**Methods:** We took advantage of a previous cohort of patients explored by the FibroScan® for the validation

of liver stiffness as a marker of fibrosis. Among them, a sub-group of patients was selected according to the following criteria: LB and FibroScan® performed within 7 days, 1. valid FibroScan® (10 measurements), 2. LB samples  $\geq 20$  mm except for patients with cirrhosis, 3. LB evaluated by two experienced pathologists (a first regular lecture for diagnosis purpose and a second lecture to quantify steatosis). 4. 228 patients were eventually selected (64% men, mean age =  $48 \pm 12$  years). The cause of the liver disease was HCV in 153, HBV in 21, alcohol in 30 and non alcoholic fatty liver disease in 24 patients. 35 patients had cirrhosis. Steatosis was quoted as: S0 steatosis  $\leq 10\%$  of hepatocytes (57% of patients), S1: 11~33% (7% of patients), S2: 34~66% (31% of patients), S3:  $\geq 67\%$  (6% of patients). Performance was evaluated in terms of Area Under the Receiver Operating Characteristic (AUROC).

**Results:** Performance in terms of AUROC is summarized in the Table.

AUROC (95% CI)	S0 vs S1S2S3 ( $\geq 11\%$ )	S0S1 vs S2S3 ( $\geq 34\%$ )	S0S1S2 vs S3 ( $\geq 67\%$ )
CAP apparent performance	0.93 (0.89-0.96)	0.95 (0.91-0.98)	0.86 (0.73-0.99)
CAP Jack-Knife cross-validation performance	0.93 (0.89-0.96)	0.95 (0.92-0.98)	0.86 (0.75-0.96)

[Table]

For the diagnosis of steatosis ( $S > 0$ ), the optimal cut-off value of the CAP provides the following results: 0.85 specificity; 0.92 sensibility; 0.82 positive and 0.93 negative predictive value. Similar results were obtained using the Jack-Knife cross-validation procedure.

**Conclusion:** The novel CAP measuring the ultrasonic attenuation inside the liver can effectively be used to detect and quantify steatosis in patients with chronic liver diseases from various causes.

**Oral Presentation APASL 2010 (March 25-28)**

**Controlled Attenuation Parameter for the detection and quantification of steatosis - Preliminary study in an alcoholic and non-alcoholic steato-hepatitis cohort**

Michel Beaugrand<sup>1</sup>, Marianne Zioli<sup>2</sup>, Victor De Ledinghen<sup>3</sup>, Catherine Douvin<sup>4</sup>, Céline Fournier<sup>5</sup>, Laurent Sandrin<sup>6</sup>, Véronique Miette<sup>6</sup>, Magali Sasso<sup>6</sup>

- 1) Hepatology, Hôpital Jean Verdier, Bondy, France
- 2) Pathology, Hôpital Jean Verdier, Bondy, France
- 3) Hepatology, Hôpital Haut-Lévêque, Pessac, France
- 4) Hepatology, Hôpital Henri Mondor, Créteil, France
- 5) Medical Affairs, Echosens, Paris, France
- 6) R&D department, Echosens, Paris, France

**Background:** Steatosis may contribute to the progression of liver fibrosis especially in Alcoholic and Non-Alcoholic Fatty Liver Disease (ALD & NAFLD) but its evaluation by non-invasive means is still a challenge. Since fat affects ultrasound propagation, a novel Controlled Attenuation Parameter (CAP) evaluated on the signals acquired by the FibroScan® has been developed. The aim of this work is to validate the CAP's performance for the detection and quantification of steatosis in a cohort of ALD & NAFLD patients.

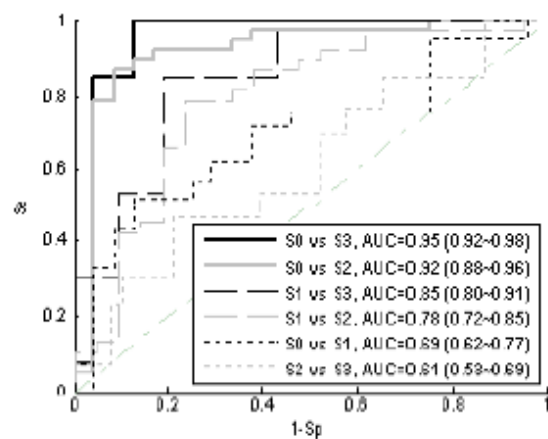
**Method:** 64 ALD and 32 NAFLD patients who underwent Liver Biopsy in 3 liver units were included. All LB were analysed by the same experienced pathologist. Steatosis was graded as: S0: steatosis  $\leq 10\%$  of hepatocytes, S1: 11~33%, S2: 34~66%, S3:  $\geq 67\%$  of hepatocytes. Repartition of patients in each grade was 25%, 22%, 40% and 13%, respectively.

**Results:** CAP was correlated to the steatosis (Spearman  $r=0.67$ ,  $p < 10^{-12}$ ). Its performance evaluated in terms of AUROC is summarized in the Table. ROC curves were also appraised between each grade, two at a time and are shown in the Figure. The CAP could effectively separate S0 from S1S2S3; S0S1 from S2S3; S0 from S2 and S3; S1 from S3 patients.

**Conclusion:** The CAP can be used to detect and quantify steatosis ALD and NAFLD patients. Performance is satisfactory especially for the detection of moderate steatosis ( $\geq 11\%$ ) and differentiation between minimal ( $\leq 10\%$ ) and severe steatosis ( $\geq 34\%$ ). Validation of this novel indicator is ongoing in a large multi-etiology cohort.

AUROC (95%CI)	S0 vs S1S2S3 ( $\geq 11\%$ )	S0S1 vs S2S3 ( $\geq 34\%$ )	S0S1S2 vs S3 ( $\geq 67\%$ )
apparent performance	0.858 (0.783-0.933)	0.867 (0.794-0.940)	0.768 (0.611-0.926)
Jack-Knife cross-validation	0.858 (0.764-0.951)	0.867 (0.788-0.946)	0.768 (0.649-0.888)

Area Under Receiver Operating Curve



**Poster AASLD 2009 (Oct. 30-Nov. 3rd)**

**Novel ultrasonic FibroScan®-based steatosis index for hepatic steatosis quantification in 618 HCV patients**

M. Beaugrand<sup>1</sup>; M. Zioli<sup>2</sup>; V. de Ledinghen<sup>3</sup>; C. Douvin<sup>4</sup>; P. Marcellin<sup>5</sup>; R. Poupon<sup>6</sup>; C. Fournier<sup>7</sup>; V. Miette<sup>7</sup>; M. Sasso<sup>7</sup>; L. Sandrin<sup>7</sup>

- 1. Hepatology, Hôpital Jean Verdier, Bondy, France
- 2. Pathology, Hôpital Jean Verdier, Bondy, France
- 3. Hepatology, Hôpital Haut Lévêque, Bordeaux, France
- 4. Hepatology, Hôpital Henri Mondor, Créteil, France
- 5. Hepatology, Hôpital Beaujon, Clichy, France
- 6. Hepatology, Hôpital Saint Antoine, Paris, France
- 7. Echosens, Paris, France

**Background and Objective:** Steatosis may contribute to the progression of liver fibrosis but its quantification by non invasive means is still a challenge.

Knowing that fat is hyperechogenic, a novel Ultrasonic Steatosis Index (USI) evaluated on the signals acquired by the FibroScan® has been developed. This indicator is based on the ultrasonic properties of radio-frequency back-propagated signals. The aim of our work is to evaluate the performance of USI in a large cohort of HCV patients.

**Patients & Method:** 618 consecutive patients with chronic hepatitis C who underwent Liver Biopsy (LB) in 5 liver units were included after a posteriori exclusion (unreliable Liver Stiffness Measurement (LSM) and LB). All LB were analysed by the same experienced hepatopathologist blind to LSM and USI results. Fibrosis was staged according to the Metavir scoring system. Prevalence of patients with significant fibrosis (≥F2) and cirrhosis was 56% and 17%, respectively. Steatosis was categorized as: S0: steatosis in less than 11% of hepatocytes, S1: 11~33%, S2: 34~100% of hepatocytes. Repartition of patients in the steatosis groups is 55%, 32%, 13% for S0, S1, S2, respectively. In addition, patients were randomly split into a training (309 patients) and a control group (309 patients).

**Results:** Using USI, results in term of AUROC are summarized in Table Results for the whole population, training and control groups. Both LSM and USI were combined for the diagnosis of steatosis through logistic regression. Results in term of AUROC are similar in the training and validation group (cf. Table Results) and are always slightly better for the combination of both LSM and USI than for USI alone.

**Conclusion:** This first study demonstrates a satisfactory performance of the novel USI to detect and quantify hepatic steatosis in CHC patients. The combination of LSM and USI slightly increases the diagnosis accuracy for the quantification of steatosis. Validity of this novel indicator has yet to be established in patients with other causes of liver disease such as alcoholic and non-alcoholic steatohepatitis.

AUROC (95% CI)	S≥1 (≥10%)	S=2 (≥34%)
USI, all patients	0.78 (0.71-0.79)	0.85 (0.79-0.90)
USI, training group	0.75 (0.68-0.81)	0.85 (0.77-0.93)
USI, control group	0.80 (0.75-0.86)	0.84 (0.76-0.92)
USI+LSM, training group	0.78 (0.72-0.84)	0.89 (0.77-0.93)
USI+LSM, control group	0.85 (0.79-0.90)	0.87 (0.81-0.94)

diagnosis and follow-up in patients with NAFLD and NASH. Knowing that fat is hyperechogenic, an Ultrasonic Steatosis Index (USI) evaluated on the signals acquired by the FibroScan® has been developed. As a first step, we evaluated the performance of this novel USI in a large cohort of HCV patients.

**Method:** 618 consecutive HCV patients who underwent Liver Biopsy (LB) in 5 liver units were included, after a posteriori exclusion of patients with unreliable Liver Stiffness Measurement (LSM) and LB. All LB were analysed by the same experienced hepatopathologist blind to LSM and USI results. Fibrosis was staged according to the Metavir scoring system. Prevalence of patients with significant fibrosis (≥F2) and cirrhosis was 56% and 17%, respectively. Steatosis was categorized as: S0: steatosis in less than 6% of hepatocytes (55% prevalence), S1: 6~10% (14% prevalence), S2: 11~33% (18% prevalence), S3: 34~100% (13% prevalence) of hepatocytes. Performance was evaluated in terms of Area Under the Receiver Operating Characteristic (AUROC) curve.

**Results:** Results are summarized in Table Results for all patients using USI for the detection of steatosis in more than 6%, 11% and 34% of hepatocytes, respectively. In a second step, half of the patients were randomly drawn into a training group where both LSM and USI were combined through logistic regression for the diagnosis of steatosis. Performance of this model was assessed in the control group made up of the other half of the patients. Results are summarized in Table Results for both training and control groups and are always slightly better for the combination of both LSM and USI than for USI alone.

AUROC (95% CI)	≥S1 (6%)	≥S2 (≥11%)	=S3 (≥34%)
USI, all patients	0.75 (0.71-0.79)	0.78 (0.71-0.79)	0.85 (0.79-0.90)
USI+LSM, training group	0.77 (0.71-0.82)	0.78 (0.72-0.84)	0.89 (0.77-0.93)
USI+LSM, control group	0.81 (0.76-0.81)	0.85 (0.79-0.90)	0.87 (0.81-0.94)
USI, training group	0.73 (0.67-0.79)	0.75 (0.68-0.81)	0.85 (0.77-0.93)
USI, control group	0.77 (0.72-0.81)	0.80 (0.75-0.86)	0.84 (0.76-0.92)

**Conclusion:** This study demonstrated a satisfactory performance of a novel USI to assess and quantify liver steatosis in a large cohort of HCV patients. The combination of both USI and LSM slightly increases the diagnosis accuracy. This new method is a promising tool for quantification of steatosis in NAFLD and NASH patients.

**Poster EASL-NASH 2009 (Sept. 23<sup>rd</sup>-26)**

**Novel ultrasonic steatosis index for steatosis quantification - Validation in a large cohort of HCV patients -**

M. Beaugrand<sup>1</sup>, M. Zio<sup>2</sup>, V. de Ledinghen<sup>4</sup>, C. Douvin<sup>5</sup>, P. Marcellin<sup>6</sup>, R. Poupon<sup>7</sup>, C. Fournier-Poizat<sup>8</sup>, V. Miette<sup>8</sup>, M. Sasso<sup>8</sup>, L. Sandrin<sup>8</sup>

- 1. Hepatology, Hospital Jean Verdier, Bondy, France
- 2. Pathology, Hospital Jean Verdier, Bondy, France
- 4. Hepatology, Hospital Haut Leveque, Bordeaux, France
- 5. Hepatology, Hospital Henri Mondor, Creteil, France
- 6. Hepatology, Hospital Beaujon, Clichy, France
- 7. Hepatology, Hospital Saint-Antoine, Paris, France
- 8. Echosens, Paris, France

**Background and Aims:** Non invasive methods to assess and quantify steatosis are still needed for

**Proceedings Article - I.E.E.E. 2009 (Sept. 19-23<sup>rd</sup>)**

**Novel Controlled Attenuation Parameter for the evaluation of fatty liver disease - A preliminary study on a large multi-etiology cohort**

M. Sasso V. Miette, L. Sandrin  
R&D Department, Echosens, Paris, France

**Introduction:** Steatosis designates the intracellular accumulation of fat in liver. Steatosis is associated with several risk factors such as obesity, diabetes, alcohol and

viral hepatitis and its prevalence is high (from 20 up to 80%) [1]. In some cases, steatosis can be associated with liver hepatitis which might cause cirrhosis. Biopsy is the gold standard for steatosis assessment. However, biopsy has potential sampling error, is invasive and might induce severe complications. Furthermore, steatosis is a silent condition and the decision for the hepatologist to refer to liver biopsy is very difficult [1]. So, there is a need for non invasive methods to assess and quantify steatosis. FibroScan® is an ultrasound-based Vibration-Controlled Transient Elastography (VCTE™) device which is used to assess liver elasticity which is related to liver fibrosis [2]. FibroScan® can be used for the detection of significant fibrosis and for the diagnosis of cirrhosis. It has been validated in many etiologies such as viral hepatic C, viral hepatitis B, alcoholic liver disease and non alcoholic liver disease. It is well known that fat affects ultrasound propagation. Indeed, fat impedance is greater than the one of soft tissues and hence in presence of fat, ultrasound signal will be attenuated. Therefore, a novel parameter measuring the ultrasonic attenuation could be of interest and might be related to steatosis. Such an indicator, named Controlled Attenuation Parameter (CAP), has been developed to process the raw ultrasonic signals stored in the FibroScan® examination file. The objective of this preliminary work is to demonstrate the feasibility of this novel CAP parameter and to assess its performance for steatosis detection and quantification on a large multi-etiology cohort.

**Patients & Method:** Patients considered in the present study were a part of the 1556 consecutive patients included in a large prospective multi-centric study carried out in 5 liver units. In this clinical study, patients were referred to Liver Biopsy (LB) whatever was the cause of the liver disease. All patients underwent both LB and Liver Stiffness Measurement (LSM) using the FibroScan®. The raw ultrasonic radio-frequency signals were stored in the FibroScan® examination file and were analyzed retrospectively, in order to evaluate the novel ultrasonic attenuation CAP. We excluded for the study the 184 patients that did not have at least 10 valid measurements in their FibroScan® exam (unreliable LSM) and the 50 patients that had clinical evidence of hepatic tumors. Only patients with hepatitis C virus (HCV) and B virus (HBV), alcoholic steato-hepatitis (ASH) and non-alcoholic steato-hepatitis (NASH) – which are the main causes of liver diseases and reference to liver biopsy– were considered here. Patients whose LB were read twice were kept (a first regular lecture by an anatomopathologist for diagnosis purpose and a second lecture by at least another or the same anatomopathologist for the purpose of a peculiar clinical study). Only 290 patients with VHC, 106 patients with VHB, 46 patients with ASH and 53 with NASH were eventually kept for the present study, corresponding to patients for whom both LB lecture results matched.

**Histologic Evaluation:** Fibrosis was evaluated in HCV and HBV patients according to the Metavir scoring

system [2]. Fibrosis in ASH and NASH patients was staged according to Brunt score [3]. Most of the time, steatosis was graded according to a percentage or range of hepatocytes with fatty accumulation or an appreciation of the anatomopathologist such as “no steatosis” or “massive steatosis”. To be able to pool all patients, steatosis was converted to the following staging: S0: no steatosis, S1: steatosis in 1~10% of the hepatocytes, S2: steatosis in 11~33% of the hepatocytes, S3: steatosis in more than 33% of hepatocytes. The repartition of the patients according to each etiology and steatosis stage is summarized *Table 1. Patients repartition according to each etiology and Steatosis stage*

Etiology	Steatosis Stage			
	S0	S1	S2	S3
HCV	145 (50%)	73 (25%)	41 (14%)	31 (11%)
HBV	63 (59%)	24 (23%)	11 (10%)	8 (8%)
ASH	—	9 (20%)	12 (26%)	25 (54%)
NASH	1 (2%)	7 (13%)	17 (32%)	28 (53%)
all patients	209 (42%)	113 (23%)	81 (16%)	92 (19%)

HCV and HBV patients are predominantly patients with no or little steatosis. ASH and NASH patients have, to the contrary, predominantly moderate to massive steatosis. To have a population where all steatosis stages are satisfactory represented, all patients from all etiologies were pooled together in the following study.

**Measurement Principle:** Ultrasonic signals were acquired using the FibroScan® probe and the examination procedure described in [4]. Measurements were performed with the standard probe which corresponds to a 3.5 MHz ultrasound transducer. Patients were lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe was covered with coupling gel and placed in the medial right intercostal space of the patients as represented Fig. 1. LSM were performed between 25 and 65 mm. Ten successful acquisitions were acquired on each patient.

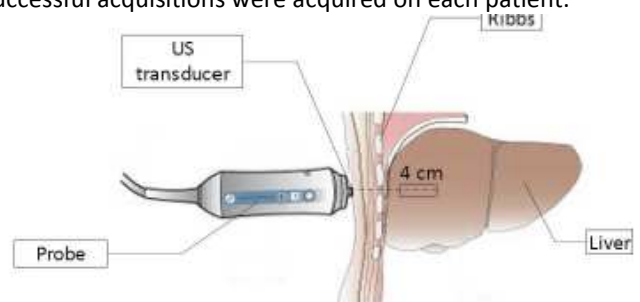


Figure 1 Measurement configuration *in vivo*.

Ultrasound attenuation was evaluated using a novel proprietary algorithm which evaluates the ultrasonic attenuation in dB/m. This parameter was named Controlled Attenuation Parameter (CAP) and is gain controlled. Ultrasound attenuation is only calculated when the LSM is valid ensuring to get an attenuation value only into the liver.

**Performance Evaluation**  
Reproducibility



The reproducibility was evaluated on 16 volunteers who underwent three consecutive exams –each exam corresponding to 10 valid measurements–. All exams were performed on each patient by the same operator. Reproducibility was evaluated using the standardized coefficient of variation (sCV) defined by [5]:

$$sCV_{\%} = \frac{P}{4\sigma_{pop}} \times 100 \quad Eq. 1$$

where  $\sigma_{pop}$  is the standard deviation of the population evaluated as the standard deviation the first examination value of each patient; and P is the measurement precision, defined as:

$$P = \sqrt{\frac{1}{N} \sum_{n=1}^N \sigma_n^2} \quad Eq. 2$$

where  $\sigma_n$  is the standard deviation of the three examination values for the patient n.

**Statistical Analysis and Evaluation of the Diagnosis Performance**

Boxplots were used to appraise the CAP distribution according to each steatosis stage. Relationship between CAP and steatosis was assessed using Spearman rank coefficient r and Kruskal-Wallis analysis of variance followed by Tuckey- Kramer multiple comparison procedure. To appraise the influence of liver fibrosis on CAP values a Kruskal-Wallis analysis of variance was performed. Note that this analysis was performed for each etiology distinctly since the fibrosis topography differs from one etiology to another. Diagnosis performances were assessed using the Receiver-Operating Characteristic (ROC) curves. Areas under the curves as well as the 95% confidence intervals were calculated using the Mann-Whitney statistic described by [6]. All the statistical analysis were performed using the R software [7] and the *ROCR* and *caTools* packages. Only statistical results associated with a p-value smaller than 0.05 were considered significant.

**Results:** CAP values evaluated on the 16 volunteers range from 195 to 359 dB/m. Elasticity range from 2.9 to 10.1 kPa. The CAP precision P and reproducibility evaluated in terms of standardized coefficient of variation sCV% are equal to 14 dB/m and 4.5%, respectively. sCV% is equal to 5.1% for the elasticity measurement.

**Relationship between CAP Values and Steatosis:**

CAP values distribution on the whole population are represented Fig. 2, according to each steatosis stage. CAP is significantly correlated to steatosis, the spearman correlation coefficient r is equal to 0.48 (p<10<sup>-17</sup>). The Kruskal-Wallis analysis of variance followed by the Tuckey-Kramer multiple comparison procedure revealed that the CAP values are significantly different from one steatosis stage to another (p<10<sup>-17</sup>).

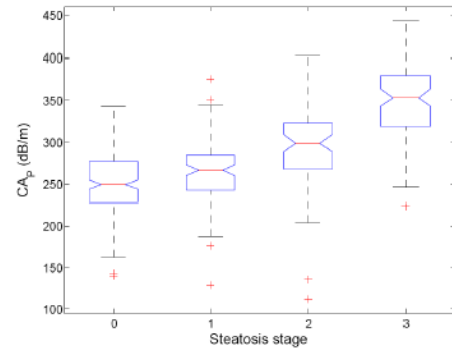


Figure 2 CAP values for each steatosis stage.

**Influence of the Fibrosis on the CAP Values:** The Kruskal-Wallis analysis of variance revealed that there is no significant influence of liver fibrosis on CAP values. Indeed, CAP values in cirrhotic patients with no steatosis is equal to 251±48 dB/m which corresponds to the averaged CAP value in all S0 patients which is equal to 249 ±45 dB/m.

**Diagnosis Performance:** Fig. 3 represents the ROC curves evaluated on the whole population, corresponding to the detection of patients from different steatosis stages: S0 versus S1, S2 and S3 patients (S<sup>≥1</sup>); S0 and S1 versus S2 and S3 patients (S<sup>≥2</sup>) and S0; S1 and S2 versus S3 patients (S=3). Corresponding area under ROC curves (AUC) and confidence interval are indicated on the figure.

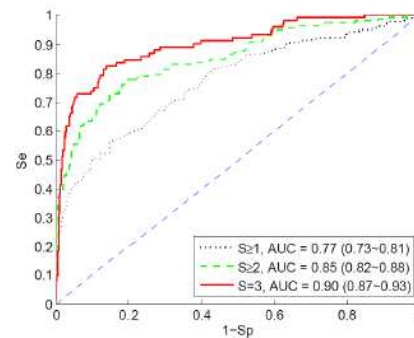


Figure 3. ROC curves and areas under curves (AUC) for the detection of steatosis stages S<sup>≥1</sup>, S<sup>≥2</sup> and S=3.

To better appraise its quantification performance, ROC curves and corresponding AUC were calculated between two steatosis stages only. For instance, ROC curve S0 versus S1 can be evaluated by only keeping patients corresponding to both S0 and S1 stages. Results for the 6 possible pairs are shown Fig. 4.

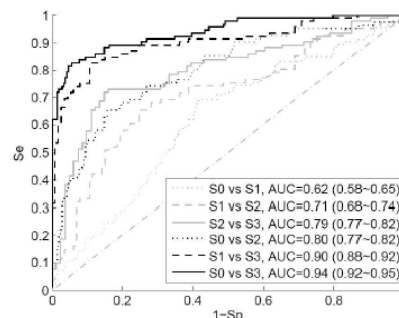


Figure 4. ROC curves and areas under curves (AUC) between each steatosis stages, two at a time.



**Discussion:** This study is a first preliminary study which demonstrates the feasibility of the use of a novel Controlled Attenuation Parameter (CAP) to detect and quantify steatosis. Performance of this indicator was assessed here on a large multi-etiology cohort of 495 patients. The CAP parameter estimates the ultrasonic attenuation in the liver according to a proprietary algorithm implemented on a peculiar set-up: the FibroScan®; ensuring the indicator to be gain controlled, operator/machine independent and exploratory volume controlled. Furthermore, the CAP was shown to be reproducible in the present study.

**Comparison with Literature:** The attenuation values obtained are similar to the ones obtained in literature. A non exhaustive revue of ultrasonic attenuation values obtained on human liver *in vivo* is given Table 2. Note that all those values were obtained on modified ultrasound scanners that were calibrated for the purpose of the study.

TABLE 2. ATTENUATION VALUES OBTAINED ON HUMAN LIVER IN VIVO

Reference	#	patient	A(3.5MHz) dB/m
[8]	18	healthy	~ 217 (63) <sup>†</sup>
	1	fatty	~ 291 <sup>†</sup>
	6	glycogen storage	~ 245 (13) <sup>†</sup>
[9]	35	healthy	~200
	7	fatty liver	~300
	7	cirrhotic	~180
[10]	44	healthy	~ 207 (34) <sup>†</sup>
	40	fatty liver	~ 280 (42) <sup>†</sup>
	20	cirrhotic	~ 217 (32) <sup>†</sup>

<sup>†</sup> estimated from results with the hypothesis of an attenuation linear with frequency and nul intercept.

**Relationship with Steatosis and Fibrosis:** The CAP parameter is correlated to steatosis and is significantly different in each steatosis stage. The CAP is not significantly different in each fibrosis stage which might indicate that ultrasonic attenuation is not influenced by fibrosis. This is consistent with the finding of other studies such as [9, 10] where they found that ultrasonic attenuation in cirrhotic patients was very close to the one in healthy patients and lower than ultrasonic attenuation in fatty liver patients.

**Diagnosis Performance:** Diagnosis performance was assessed here on a large multi-etiology cohort of 495 patients and was found to be correct for the detection of steatosis (S<sup>3</sup>1), good for the detection of more than 10% fatty deposit (S<sup>3</sup>2) and excellent for the detection of more the 33% of steatosis (S<sup>3</sup>3). Quantification performance of the novel CAP parameter can be appraised Fig. 4. It can be observed that CAP performs: poorly for the differentiation of S0/S1 and S1/S2, satisfactorily for the differentiation of S2/S3, S0/S2 and S1/S3 and effectively for the differentiation of S0/S3 and S1/S3. The ability of the CAP indicator to detect and quantify steatosis are satisfactory. However, it should be pointed out that performance was assessed taking a reference made according to the matching indications made by two anatomopathologists. Performance of the

CAP has to be assessed on a large cohort where steatosis is histologically staged according to a precise methodology, possibly by the same anatomopathologist or by a double blind reading. Furthermore, it is important to note that liver biopsy present potential sampling error.

**Conclusion:** A novel CAP parameter was developed which estimates the ultrasonic attenuation according to a proprietary algorithm implemented on a peculiar set-up: the FibroScan®. The CAP parameter presents the advantages to be:

- easy to evaluate even for an operator that does not have any ultrasound imaging skills,
- evaluated in the liver and corresponds to the evaluation of the same liver volume than the LSM,
- quasi immediate (with no significant modification of examination time regarding to a regular FibroScan® exam),
- gain controlled,
- operator / machine independent,
- reproducible.

Performance of this novel CAP parameter was assessed here in a preliminary study on a large multi-etiology cohort. Results are very promising for the detection and quantification of steatosis. However, its performance has to be validated into specific etiologic groups. Influence of the steatosis topography (micro/macro vesicular, homogeneous, heterogeneous etc.) and other histologic constituents, such as ballooning degeneration or Mallory bodies, specific to each etiology has to be considered. Large cohorts are required to determine appropriate threshold to detect and quantify steatosis. This novel CAP parameter could be implemented together with LSM in a new device which would be able to evaluate two physical parameters:

- the elasticity (E, in kPa) which is related to fibrosis,
- the ultrasonic attenuation (CAP) which is related to steatosis.

Those two physical parameters appraised simultaneously, in the same liver volume, which might have the potential to improve liver diseases evaluation. In particular, combination of both parameters might be useful to diagnose non alcoholic steato-hepatitis which is a silent disease due to metabolic dysfunctions which combines steatosis and necro-inflammatory liver lesions and possibly fibrosis [1].

**Poster I.E.E.E. 2009 (Sept. 19-23<sup>rd</sup>)**

**Development of an ultrasonic steatosis index for the evaluation of fatty liver disease**

M. Sasso V. Miette, L. Sandrin

R&D Department, Echosens, Paris, France

**Background, Motivation and Objective:** Steatosis designates the intracellular accumulation of fat in liver. The worldwide prevalence of steatosis is very high (from 20 up to 80%) and is associated with several risk factors such as obesity, diabetes, alcohol, viral hepatitis. In many cases, steatosis can be accompanied with liver hepatitis

which might induce cirrhosis. Biopsy is the gold standard for steatosis assessment. However, biopsy has a potential sampling error, is invasive and might induce severe complications. Furthermore, steatosis is a silent condition and the decision for the hepatologist to refer to biopsy is often difficult. FibroScan® is an ultrasound-based transient elastography system that can be used for the diagnosis of liver fibrosis and cirrhosis by measuring the liver stiffness. The objective of this work is to demonstrate the feasibility of a novel Ultrasonic Steatosis Index using our vibration-controlled transient elastography device.

**Statement of Contribution/Methods:** An Ultrasonic Steatosis Index (USI) has been developed based on the ultrasonic properties of the radio-frequency back-propagated signal. This index is evaluated between 25 and 65 mm, in the same zone as the liver stiffness measurement using the M-probe of the FibroScan®. The ability of this index has been evaluated in a retrospective study including 345 patients in four etiologic groups: 171 with Viral Hepatitis C, 64 with Viral Hepatitis B, 56 with alcoholic and 55 with non-alcoholic liver disease. All patients' livers were assessed using both FibroScan® and histology. Steatosis was quantified on the biopsy as the percentage of hepatocytes with macrovesicular accumulation of fat (S0: 0% of hepatocytes, S1: 1~10%,

S2: 11~33%, S3 > 34%). Performance of the USI is appraised using the AUROC (Area Under the Receiver Operating Curve), taking the histological quantification of liver steatosis as gold standard.

**Results:** Using the USI, AUROC is equal to 0.84 and 0.93, in alcoholic and non-alcoholic liver disease, respectively, for the detection of more than 34% of steatosis (S3). In VHC (VHB, resp.) AUROC is equal to 0.73 (0.82, resp.) for the detection of more than 1% of steatosis, 0.92 (0.93, resp.) for the detection of more than 11% of steatosis and 0.90 (0.93, resp.) for the detection of more than 34% of steatosis. Results indicate that the USI might detect steatotic liver from 10% of cells infiltrated with fat.

**Discussion and Conclusions:** This preliminary study shows the potential of the USI to diagnose hepatic steatosis. A larger retrospective clinical study is currently conducted in 830 patients (700 VHC, 90 with alcoholic liver disease and 40 with non-alcoholic liver disease) where some threshold would be determined for the quantification of steatosis. In addition, the influence of steatosis on the liver stiffness measurement will be analysed. The combination of both USI and liver stiffness measurement evaluated using the FibroScan® might discriminate patients from simple steatosis to patient with steatohepatitis lesions.

