

## Quantification of Steatosis and Fibrosis using a new system implemented in an ultrasound machine

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### Abstract

**Aim:** The study compared the usefulness of 2D-SWE and attenuation measurements obtained using Aplio i800 from Canon together with Transient Elastography (TE) and the Controlled Attenuation Parameter (CAP) as the reference method. **Material and methods:** We included 112 consecutive adults with reliable LS measurements, 44 healthy subjects and 68 subjects with chronic hepatopathies in whom liver stiffness (LS) and steatosis were evaluated in the same session employing two elastography techniques: Transient Elastography (TE) with Controlled Attenuation Parameter (CAP) implemented on the FibroScan® 530 Compact system and Two Dimensional Shear Wave Elastography (2D-SWE) with Attenuation Imaging (ATI) installed on the Aplio i800 series ultrasound system. Reliable measurements were defined as the median value of 10, respectively 5 valid LS measurements for TE and 2D-SWE, with an interquartile range interval/median ratio (IQR/M) <30%. **Results:** A very strong positive correlation was found between LS values obtained by TE and 2D-SWE:  $r=0.88$ ,  $p<0.0001$  and between the attenuation coefficients of steatosis obtained by CAP and ATI,  $r=0.81$ ,  $p<0.0001$ . The best cut-off values by 2D-SWE for predicting different stages of liver fibrosis were: for  $F\geq 2$  - 7.9 kPa and  $F=4$  - 11.7 kPa. Regarding steatosis, the best ATI cut-off values were: for  $S\geq 1$  - 0.79 dB/cm/mHz and for  $S3$  - 0.86 dB/cm/mHz. **Conclusion:** 2D-SWE and ATI measurements with the new system strongly correlated with TE and CAP results.

**Keywords:** liver steatosis; liver fibrosis; liver stiffness; multiparametric ultrasound

### Introduction

In the field of hepatology, the burden of liver diseases continues to grow, especially in the developed world. Differences in liver disease epidemiology occur in part because of the prevalence of modifiable risk factors, such as obesity, viral hepatitis and harmful alcohol consumption [1]. Chronic hepatitis C is now cured with a very high success rate, following a short-duration treatment (weeks) with direct-acting antiviral agents (DAAs), while chronic hepatitis B infection is controlled with

nucleoside/nucleotide analogs. There has been a general increase in the prevalence of non-alcoholic fatty liver disease (NAFLD) in clinical practice, especially in some categories of patients such as obese, type 2 diabetics, patients with metabolic syndrome or dyslipidemia. It is currently estimated that the global prevalence of NAFLD is as high as 1 billion [2]. NAFLD encompasses a wide histological variety: nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), fibrosis, NASH cirrhosis and NASH-related hepatocellular carcinoma (HCC).

NAFLD is characterized by hepatic fat accumulation in more than 5% of the hepatocytes, in the absence of any secondary causes and is a diagnosis of exclusion [3]. The spectrum of fatty liver can go from non-evolutionary simple steatosis to the progressive non-alcoholic steatohepatitis (NASH), with inflammation, ballooning and fibrosis in histology [4]. The increasing prevalence of NAFLD with advanced fibrosis is concerning because patients appear

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to experience higher liver and non-liver related mortality than the general population [3].

Liver biopsy (LB) is the recommended method to differentiate simple steatosis from progressive steatohepatitis [5], but considering the large number of cases with NAFLD, LB is not feasible as a diagnostic tool in such a large population. Thus, noninvasive methods are necessary for the assessment of liver fibrosis and steatosis. Several methods - Transient Elastography (TE), point Shear Wave Elastography (pSWE) and Two-Dimensional Shear Wave Elastography (2D-SWE) [5-9] - are used for the assessment of liver fibrosis in such patients. The Controlled Attenuation Parameter (CAP), implemented on the FibroScan device (Echosens, Paris, France) was firstly used for the noninvasive assessment of steatosis severity and has shown a correlation with histologic grades in adults [10-12]. Several guidelines have recommended CAP as an accurate alternative to abdominal ultrasonography for the detection of hepatic steatosis [13,14]. In the latest WFUMB guidelines on ultrasound elastography, CAP has been recommended as a point-of-care, standardized and reproducible technique for the detection of liver steatosis [15], although, its accuracy may be affected by variations in cut-off values of different steatosis grades and different covariates [16].

In the last few years, different producers of ultrasound systems (Hitachi, Canon, General Electric) developed technologies able to quantify steatosis and fibrosis [17-22]. Some of them have the option to evaluate also viscoelastic tissue properties for the assessment of inflammation (Hitachi, Canon).

Our study aims to evaluate the usefulness of 2D-SWE (Aplio i800 from Canon Medical Systems) for the non-invasive assessment of liver fibrosis and steatosis, using Transient Elastography (TE) with the Controlled Attenuation Parameter (CAP) as the reference standard in a cohort of subjects.

## Material and methods

### Study population

The study cohort was composed of 112 consecutive adults with reliable LS measurements, 44 healthy subjects and 68 subjects with chronic hepatopathies. The inclusion criteria for healthy subjects were: age older than 18 years, with normal biological tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin,  $\gamma$ -glutamyltranspeptidase, alkaline phosphatase) and LS values by TE  $<7$  kPa [6,23-25]. For subjects with chronic hepatopathies, the inclusion criteria were: age older than 18 years, documented history of any chronic hepatopathies. We excluded patients undergoing antiviral treat-

ment, patients with ascites, patients with signs of biliary obstruction and liver congestion secondary to heart failure and patients with focal liver lesions.

The diagnosis of NAFLD was based on the latest guidelines established by the American Association for the Study of Liver Diseases [14] as follows: (i) fatty change of the liver observed by imaging; (ii) no heavy alcohol consumption (ethanol intake  $<210$  g per week for men and  $<140$  g per week for women); (iii) no other factors inducing fatty changes of the liver such as medications; and (iv) no chronic liver disease with clear etiology (hepatitis B virus, hepatitis C virus), primary biliary cholangitis, primary sclerosing cholangitis or autoimmune hepatitis.

All subjects signed an informed consent for elastographic measurements and biological tests. The study was approved by the Ethics Committee and institutional review board of "Victor Babeş" University of Medicine and Pharmacy and was performed according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

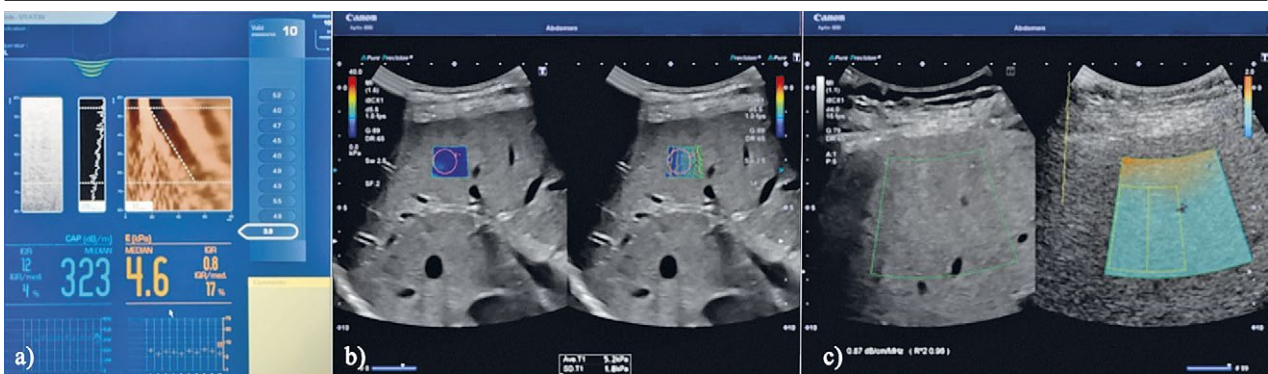
### Methods

Liver stiffness (LS) and steatosis were evaluated in the same session employing two elastography techniques: TE with Controlled Attenuation Parameter (CAP) implemented on the FibroScan® 530 Compact system (Echosens, Paris, France) and 2D-SWE with Attenuation Imaging (ATI) installed on the Aplio i800 series ultrasound system (Canon Medical Systems Corporation, Otawara, Tochigi, Japan).

### Transient Elastography and Controlled Attenuation Parameter

TE was performed in fasting conditions for more than 4 hours (fig 1a), with each patient in supine position, right arm in maximum abduction, by intercostal approach, in the right liver lobe. In each patient, we aimed for 10 valid LS measurements, using the M probe (standard probe - transducer frequency 3.5 MHz) or the XL probe (transducer frequency 2.5 MHz). M and XL probes were used according to the EFSUMB recommendation on M and XL probe selection [26]. The median value of 10 valid LS measurements was calculated and the results were expressed in kilopascals (kPa). Reliable measurements were defined as the median value of 10 valid LS measurements, with an interquartile range interval/median ratio (IQR/M)  $<30\%$  [27-29].

To discriminate between fibrosis stages, we used the following TE cut-off values [6,23-25]:  $F \geq 1$  - 7 kPa,  $F \geq 2$  - 8.4 kPa and  $F = 4$  - 13.2 kPa. To discriminate between steatosis stages, we used the CAP cut-off values recommended by a recent meta-analysis performed by Edlowes et al: S1 (mild) - 274 dB/m, S2 (moderate) - 290 dB/m, S3 (severe) - 302 dB/m [30].



**Fig 1.** Methods used for liver evaluation: a) Transient Elastography (TE) and Controlled Attenuation Parameter (CAP) with the Fibroscan device. Sample display showing the echo M-scan on the left, single-line amplitude A-scan in the middle, and the displacement M-mode after a vibration-controlled impulse push on the surface on the right. Numeric values for CAP are displayed on the left side (db/m) and for TE on the right side (kPa); b) Illustration of a 2D-SWE measurement performed using Aplio i800 from Canon with elasticity map displayed on the left and propagation map displayed on the right. Numeric results expressed in kPa are displayed on the bottom of the image; c) Illustration of an Attenuation Image (ATI) acquisition using Aplio i800 from Canon with B-mode image displayed on the left and color-coded acquisition box with region of interest (ROI) displayed on the right. Numeric values expressed in dB/cm/MHz are displayed on the bottom of the image.

### 2D-Shear Wave Elastography and Attenuation Imaging

LS evaluation by 2D-SWE was performed using the Multi-Frequency Slim Face Convex PVI-475BX (i8CX1) 4 MHz probe (fig 1b). All measurements were performed in fasting conditions for at least 4 hours, with the patient in the supine position, right arm in maximum abduction, by intercostal approach, in the right liver lobe. The probe was applied perpendicular to the liver surface, in the best acquired acoustic window, with the shear wave (SW) measurement box placed at least 1 cm below the liver capsule. The patients were asked to hold their breath for a few seconds, without deep inspiration before breath-hold. Since there are no published studies regarding reliability criteria using Aplio i800, we followed the acquisition protocol recommended by the manufacturer: region of interest (ROI) shape/size - circle/10 mm diameter, the center of ROI at a depth not greater than 5 cm, placement of ROI on the most parallel propagation map area. Reliable LS measurements were defined as the median value of 5 measurements performed in a homogeneous area of liver parenchyma, with an IQR/M <30%.

For Attenuation Imaging (ATI) (fig 1c) we followed the acquisition protocol proposed by the manufacturer: patient in supine position, same intercostal window as SW, probe perpendicular to the liver surface, freeze when image included parenchyma free of artifacts, shadows, or large vessels. ATI ROI was placed just below the orange liver capsule artifact. Reliable ATI measurements were defined as the median value of 5 measurements performed in a homogeneous area of liver parenchyma, with an IQR/M <30% and  $R^2 > 0.90$  (displayed in white below

the greyscale image, which is a quality parameter recommended by the manufacturer). The system automatically calculated the median value and IQR of the valid measurements.

Liver viscoelasticity is assessed by the Aplio i800 ultrasound system using: SW speed (m/s), SW Elasticity (kPa), Dispersion slope related to viscosity (m/s)/kHz, while steatosis by Attenuation Imaging (ATI) (dB/cm/MHz).

### Statistical analysis

The statistical analysis was performed using SPSS software v.17 (SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel 2019. The Kolmogorov-Smirnov test was used for testing the distribution of numerical variables. Descriptive statistics were used for clinical, anthropometric and demographic data of the patients. Numerical variables with normal distribution are presented as means  $\pm$  standard deviation, while variables with non-normal distribution are presented as median values and range. The Kolmogorov-Smirnov test was used for testing the distribution of numerical variables. Qualitative variables were presented as numbers and percentages.

The differences between the groups were assessed using a student's t-test for continuous variables with normal distribution, Mann-Whitney U's test for continuous variables without normal distribution. Fisher test and Pearson's chi-squared test for proportions.

Areas under the receiver-operating characteristic (AUROC) curves were calculated for ATI and 2D-SWE from Canon to identify the cut-off values for various stages of liver fibrosis and steatosis. Positive predictive value (PPV – true positive cases/all positive cases), negative

predictive value (NPV – true negative cases/all negative cases) were calculated [31]. 95% confidence intervals were calculated for each predictive test and a p-value < 0.05 was considered as significant for each statistical test. For correlations, we used the Spearman’s coefficient. For comparing the new technique with TE we used the Pearson coefficient of precision.

**Results**

Patients characteristics are presented in Table I.

Mean LS values assessed by 2D-SWE were similar with mean LS values assessed by TE (7.21±4.3 vs 7.47±8.13, p=0.66) (fig 2).

For healthy volunteers, mean LS values by 2D-SWE was 5.15±2.61 kPa and by TE was 5.47±2.53 kPa, p=0.5.

A very strong positive correlation was found between the LS values obtained by TE and 2D-SWE: r=0.88, p<0.0001 and between the attenuation coefficients evaluating steatosis (CAP vs. ATI, r=0.81, p<0.0001).

According to the Bland-Altman test, the mean difference between TE and 2D-SWE was 0.3±0.01. The 95% upper and lower LOA were 12.6 and -12.1 kPa, respectively (fig 3).

Table I. Patients characteristics (N=112)

Parameter	
Age (years)	57 (25-83)
BMI (kg/m <sup>2</sup> )	29.3 (18.3-58.4)
ALT (IU/ml)	30.5 (7.6-160)
AST (IU/ml)	24 (8-180)
GGT (IU/ml)	53 (20-1501)
ALP (IU/ml)	83.5 ± 35.1
Platelets count/mm <sup>3</sup>	221 ± 82.379
Liver disease etiology	
Healthy subjects	44 (39.3)
NAFLD	59 (52.7)
Alcoholic Liver Disease (ALD)	2 (1.8)
Hepatitis B virus	4 (3.5)
Hepatitis C virus	3 (2.7)
Fibrosis stage (N=68)	
F<2	46 (67.4)
F2-3	9 (13.2)
F4	13 (19.4)
Steatosis grade (N=68)	
S0	22 (32.3)
S1	7 (10.2)
S2	4 (5.8)
S3	35 (51.7)

The results are expressed as number (%), median (range) or mean ± standard deviation. BMI: Body Mass Index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-Glutamyltranspeptidase; ALP: alkaline phosphatase

For the performance analysis, we used only the group with hepatopathies, excluding the healthy volunteers. The best cut-off values for discriminating among stages of liver fibrosis by 2D-SWE are presented in Table II and their performance is shown in figure 4.

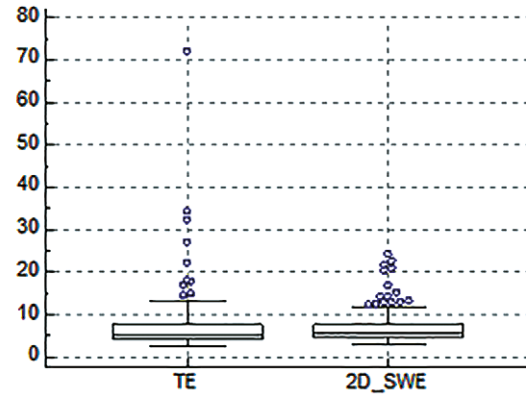


Fig 2. Box-plot graphic for mean LS values assessed using TE and 2D-SWE showing the differences between them and how the values spread. The box-plots indicate the interquartile ranges (boxes), medians (thick lines inside boxes), ranges (vertical lines).

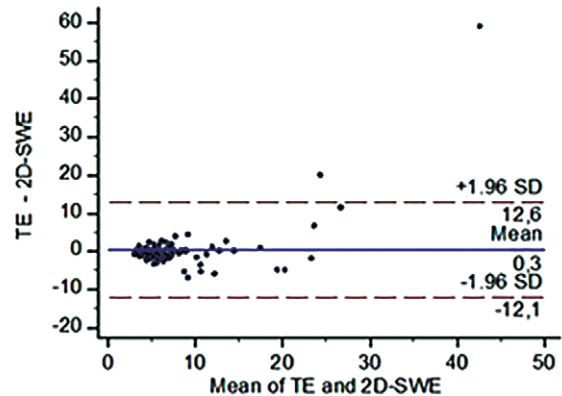


Fig 3. Bland-Altman plot of TE and 2D-SWE. The solid line represents the mean of the difference in the LS values. The dashed lines define the LOA. The 95% upper and lower LOA were 12.6 and -12.1, respectively.

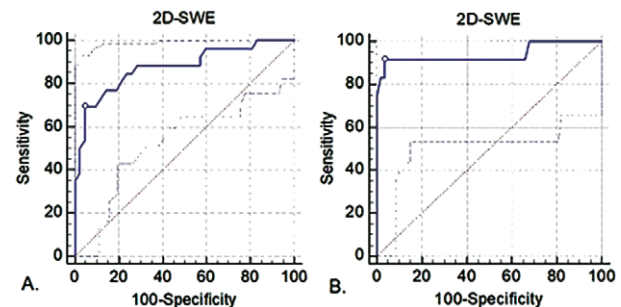


Fig 4. A. AUC performance of liver fibrosis stage F≥2; B. AUC performance of liver fibrosis stage F=4

Table II. 2D-SWE cut-off values for staging different grades of liver fibrosis.

Fibrosis stage	Cut-off	Se	Sp	NPV	PPV	+LR	-LR	AUC	p-value
F $\geq$ 2	7.9 kPa	69.2%	95.2%	83.3%	90.0%	14.54	0.32	0.89	<0.0001
F=4	11.7 kPa	91.6%	96.4%	98.2%	84.6%	25.67	0.08	0.94	<0.0001

Se: sensitivity; Sp: specificity; NPV: negative predictive value; PPV: positive predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio; AUC: area under receiver-operating characteristics curve

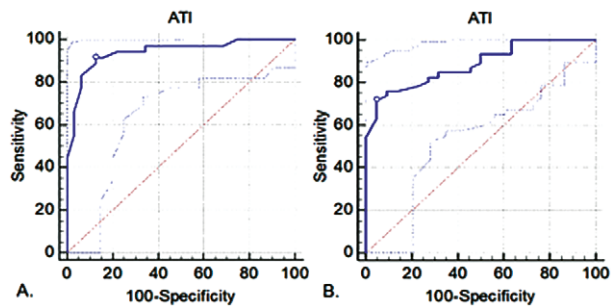


Fig 5. A. AUC performance for steatosis grade S3; B. AUC performance for steatosis grade S $\geq$ 1.

Regarding steatosis, the best cut-off values by ATI were: for S $\geq$ 1 - 0.79 dB/cm/mHz (AUROC 0.88; Se=71.7%; Sp=95.4%, PPV=97.1, NPV=61.8%), for S3 - 0.86 dB/cm/mHz (AUROC 0.94; Se=91.6%; Sp=87.5%, NPV=90.3, PPV=89.2) (fig 5).

## Discussion

Our study reveals that liver fibrosis and steatosis assessment with the Aplio i800 ultrasound system from Canon is a highly feasible method.

Published papers evaluating 2D-SWE systems have shown good correlations with liver histology or TE [18,32-35]. In a previous study performed by Hermann et al [33], which included 1134 patients with mixed chronic liver disease and where liver biopsy was used as a reference method, 2D-SWE demonstrated excellent diagnostic accuracies for all fibrosis stages in patients with hepatitis C, hepatitis B and NAFLD (AUROC 0.86, 0.90, 0.85 for diagnosing significant fibrosis and AUROC 0.92, 0.95, 0.91 for diagnosing cirrhosis, respectively). Moreover, the AUROC of 2D-SWE was 0.022-0.084 larger than the AUROC of TE for diagnosing significant fibrosis (p=0.001) and 0.003-0.034 for diagnosing cirrhosis (p=0.022) in all patients. This corresponds reasonably well with our results with AUROCs of 0.89 and 0.94 for diagnosing significant fibrosis, respectively for diagnosing cirrhosis.

In another study, performed by Cassinotto et al [32], which included 291 patients with NAFLD and compared the performance of 2D-SWE, TE and Virtual Touch

Quantification (VTQ) using the liver biopsy as a reference method, 2D-SWE had AUROCs of 0.86, 0.89 and 0.88 for the diagnosis of significant fibrosis, severe fibrosis and liver cirrhosis, respectively, results which are similar to the AUROCs of 0.89 and 0.94 for significant fibrosis, respectively cirrhosis observed in our study. Pairwise comparisons of AUROC values between SSI, FibroScan, and VTQ(ARFI) were performed on 231 patients, and 2D-SWE showed similar diagnostic performance for the diagnosis of significant fibrosis, severe fibrosis, respectively cirrhosis (all p=0.5), whereas the difference between 2D-SWE and TE correlation coefficients was not significant ( $r^2=0.72$  versus 0.67; p=0.1), results which are similar to our study, where LS values measured by 2D-SWE from Canon strongly correlated with those obtained by TE:  $r=0.88$ , p<0.0001. Furthermore, based on TE cut-off values proposed by Roccarina et al [25], Friedrich-Rust et al [6], Kumar et al [23] and Imajo et al [24], we were able to propose 2D-SWE cut-off values for different stages of fibrosis in this cohort of patients. The AUROCs for various stages of fibrosis are very good, increasing with the progression of fibrosis severity.

Regarding quantification of steatosis severity, we considered CAP as a reference method using the cut-off values proposed by Eddowes et al 2019 [30], although published studies have failed to establish uniformly accepted cut-off values for CAP in differentiating between steatosis grades [8,9,36]. In our study, we observed a very good correlation of ATI from Canon with CAP:  $r=0.81$ , p<0.0001. On the other hand, we were able to calculate ATI cut-off values for ruling in mild steatosis and ruling out severe steatosis, which is most important in clinical practice. The ATI values increase with the severity of steatosis. Few studies evaluated this parameter, one recent study was performed by Tada et al [37], where, in a cohort of patients with histologically diagnosed steatosis, the method showed good diagnostic capability for the detection of hepatic steatosis and ATI values significantly increased with increasing steatosis grade in patients with NAFLD (p<0.001). Furthermore, the diagnostic values of ATI for steatosis grades  $\geq$ 1,  $\geq$ 2, and 3 in NAFLD patients were 0.77, 0.88 and 0.86, which are similar to our results, where we obtained AUROCs of 0.88, 0.94 for diagnosing steatosis grades  $\geq$ 1 and 3 [37].

What are the advantages of ultrasound systems that include modules for liver stiffness and liver steatosis? These machines are very important for „point of care” ultrasound, where, in the consultation room, in 10-15 minutes we can make an imaging assessment of the liver (structure, steatosis, masses) and, if needed, we can immediately perform quantification of liver stiffness and steatosis.

However, our paper has some limitations. The first is that liver biopsy or Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) was not available for the evaluation of these patients and only another elastography technique was used as a reference, although lately, many published studies have been using FibroScan with CAP as a reference method when comparing the performance of different elastography techniques. Another limitation of our study is the relatively small number of patients, with a low prevalence of liver cirrhosis and intermediate stages of fibrosis and steatosis which could have had an impact on the results; it would be interesting to see if these results hold in larger groups of patients. On the plus side, we were able to calculate cut-off values for liver stiffness and ATI using this new system.

We consider that it is time for these multiparametric ultrasound systems to enter clinical practice because they can offer valuable information about the liver in a short time. They can be used by hepatologists, internal medicine specialists or radiologists, allowing a complex evaluation of the liver in a few minutes.

In **conclusion**, this new ultrasound system that can quantify liver fibrosis and steatosis seems to be ready for clinical practice. 2D-SWE and ATI measurements with the new system strongly correlate with TE and CAP results.

**Conflict of interest:** none.

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