Sonographic Elasticity Imaging of Acute and Chronic Deep Venous Thrombosis in Humans

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Objective. The purpose of this study was to assess the ability of sonographic elasticity imaging to distinguish acute from chronic deep venous thrombosis (DVT). ***Methods.*** Fifty-four patients, 26 with acute DVT and 28 with chronic DVT, were studied, and we analyzed the data in 46 patients, 23 with acute (mean age, 5.7 days) and 23 with chronic (>8 months) DVT. Scanning was performed with a 5-MHz linear array transducer during continuous freehand external deformation of each thrombus using the ultrasound scan head. The strains in the thrombi were normalized to the average strain between the skin surface and the back wall of the vein. Relative thrombus echogenicity was measured by comparing the echogenicity of the thrombus with that of the adjacent arterial lumen. Statistical analyses were performed with the Mann-Whitney *U* test and receiver operating characteristic analysis. ***Results.*** The median normalized strain magnitude for the acute cases was 2.75, with an interquartile range of 2.4 to 3.71, whereas the median normalized strain magnitude for the chronic cases was 0.94, with interquartile range of 0.48 to 1.36. The difference was highly significant ($P < 10^{-7}$). The area under the receiver operating characteristic curve (A_z) was 0.97 ± 0.02 (SE). The echogenicity difference between the populations was highly significant ($P < 10^{-5}$), with A_z of 0.92 ± 0.04. The difference between the A_z values was not significant ($P > .05$). ***Conclusions.*** In this population, sonographic elasticity imaging performs at least as well as thrombus echogenicity. Thrombus aging using elasticity imaging would be particularly helpful in evaluating symptoms in patients with post-thrombotic syndrome. ***Key words:*** deep venous thrombosis; elastography; sonographic elasticity imaging; strain imaging.

Abbreviations
DVT, deep venous thrombosis; IQ, in-phase and quadrature; IQR, interquartile range; ROC, receiver operating characteristic; 2D, 2-dimensional

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Deep venous thrombosis (DVT) is a major clinical problem, with more than 2 million Americans affected annually.[1,2] The problem is amplified by the combined incidence of DVT and pulmonary embolism in at least 600,000 patients per year, leading to as many as 60,000 deaths in the United States alone.[2]

In many situations, the diagnostic method of choice for DVT is venous duplex sonography, which combines compression sonography augmented with color flow Doppler imaging,[3] even though venography is still regarded as the reference standard.[4,5] With the addition of color flow to venous compression gray scale imaging, the sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of acute DVT in symptomatic patients are all greater than 95%.[6]

However, there are certain circumstances in which venous duplex imaging has limitations, and one is in patients who have had previous DVT and have new symptoms shortly after initial treatment. In these patients, it is often difficult to differentiate acute from organized chronic thrombi.[3,7–10] This differentiation is required to recommend treatment. A new episode of acute DVT is treated with heparin or low-molecular-weight heparin followed by oral anticoagulant therapy.[11] However, the presence of a chronic thrombus in a symptomatic patient without a new acute thrombus would suggest post-thrombotic syndrome, which does not require anticoagulant therapy unless an acute thrombus is present.[12] Hence, given this scenario, it becomes very important to be able to distinguish between pure post-thrombotic syndrome and the new development of acute DVT with or without post-thrombotic syndrome.

Therefore, determining the maturity of a DVT is crucial for therapeutic management. Some authors suggest that the critical maturation, typically assessed through thrombus age, seems to occur at about 5 to 10 days after formation and is thought to be caused by the contraction and polymerization of strands of fibrin.[13] Other authors have approximated the separation between acute and chronic DVT at 14 days.[14,15] Even given these results, however, there are still no good techniques for aging a thrombus.

One very promising technique for estimating thrombus age is sonographic elasticity imaging.[16,17] This is because sonographic elasticity imaging directly assesses tissue hardness,[18,19] and it is well accepted that DVTs harden as they age.[13] For example, organized, mature thrombi in superficial veins are said to feel like a "rope" in a patient's thigh.[3] Thus, in some sense, sonographic elasticity imaging would represent a natural method for determining DVT maturity and would potentially be a means of distinguishing post-thrombotic syndrome with a chronic DVT from a newly formed acute DVT. This supposition is further supported by controlled animal studies in our laboratory and others in which sonographic elasticity imaging could very accurately assess the ages of experimentally induced thrombi.[16,17,20,21] However, up until now, the ability to determine the age of DVT with sonographic elasticity imaging in humans has only been shown in 2 patients.[22] In this report, we present a larger patient series.

Materials and Methods

This study was approved by the University of Michigan Investigational Review Board, and all patients signed an informed consent document before participating. This was a prospective study.

Patient Population

Fifty-four patients participated in the study. There were 26 patients with acute DVT, mean age, 56.6 years, with a range of 21 to 81 years and 28 patients with chronic DVT, mean age, 59.4 years, with a range of 27 to 89 years. Of the patients with acute DVT, 11 were male and 15 were female. The chronic group contained 15 male and 13 female patients. Seventeen of the acute thrombi were in the popliteal vein or above, whereas 9 were calf vein thrombi. Of the acute thrombi that were at or above the popliteal vein, 10 were partially occluding, and 7 were totally occluding. Of the 9 calf vein acute thrombi, 7 were partially occluding, and 2 were totally occluding. For the patients with chronic DVT, 27 thrombi were in the popliteal vein or above, and 1 was a calf vein thrombus. All the chronic thrombi were partially occluding the vein.

The patients with acute DVT composed 2 groups. The first was derived from 194 patients who were scheduled for either hip or knee replacement surgery. These patients were recruited consecutively without bias. No patients had histories of DVT. Before their operations, each had lower extremity sonographic scans to rule out DVT, and none was found. In 4 of these patients, symptoms of DVT developed, and lower extremity DVTs were proven by venous sonographic scans within 2 weeks of their surgery.

Given the low fraction of patients in whom DVTs developed in the first group, we found it necessary to expand the acute group to include any patient with DVT proven by venous sonography who had no history of DVT and who had symptoms or signs of DVT for 14 days or less. The patients were identified by technologists working in the Diagnostic Vascular Laboratory of the University of Michigan Department of Surgery, who were aware of the study criteria. When technologists identified patients who met the study criteria, they notified one of the authors (J.M.R. or W.F.W.) or the study coordinator. On the basis of this sampling method, these patients were consecutive.

It should be noted that using the onset of signs and symptoms is a typical method for defining initiation of DVT in the literature.[8,15,23,24] We chose 14 days as a reasonable upper bound on the age of acute DVT.[14,15] Other authors have picked earlier time separations between acute and chronic DVTs,[13] but for this study, we chose the more conservative boundary of 2 weeks. Our goal was to have a group of indisputably acute thrombi that we could compare with indisputably chronic thrombi, which in our case were all at least 8 months old (see below). This would emulate the clinical situation in which a patient with a previously diagnosed DVT returns with a new acute DVT. We would like to be able to discriminate between acute and chronic thrombi in that case, and given that thrombi are known to harden over time in animals and humans,[3,13,16,17,20,21] choosing the later threshold for acute thrombi would only tend to decrease whatever hardness difference existed between acute and chronic groups. The acute group included 22 patients.

The chronic group contained 26 patients with proven lower extremity DVTs by venous sonography of at least 1 year in age and had recent lower extremity sonography as part of a protocol for assessing an implanted Greenfield inferior vena cava filter (Boston Scientific, Natick, MA). We attempted to recruit every patient from the monthly lists of patients scheduled to undergo follow-up examinations as part of the vena cava filter study during a 1-year period from November 2002 through October 2003. In each of the recruited patients, the latest follow-up sonographic scan showed only the previously diagnosed DVT. Two additional patients with proven chronic thrombi were also recruited on the basis of a facsimile broadcast sent to local physicians. Both of these patients had thrombi proven by venous duplex sonography. One of these patients had a thrombus of at least 8 months' duration, whereas the other patient's thrombus was 2 years old. No patients with chronic DVT had new symptoms or signs of acute DVT at the time of the diagnostic scans.

Scanning Technique and Data Acquisition

Each patient was scanned in the standard position for a compression sonographic study given the location of their thrombus. The scanning technique was exactly analogous to that used in standard diagnostic venous sonographic scans. Scans were performed using a Sonoline Elegra sonographic scanner (Siemens Medical Solutions, Mountain View, CA) capable of capturing frames of digital phase-sensitive ultrasound signals. We used a 5-MHz (5.0 HDPL 40) linear array transducer for both compression and imaging. The thrombus-containing veins were scanned in a transverse orientation, and we scanned at multiple sites across the thrombi. Before each deformation, we performed a color Doppler scan to determine whether there was any flowing blood adjacent to the imaged thrombus. If flowing blood was detected, we preloaded the deformation by pushing on the tissue with sufficient force to collapse the blood-containing portions of the vein. The number of sites at which we deformed a thrombus varied depending on the size of the thrombus; however, the sites were separated by at least 1 cm, which was greater than the elevational width of the scan head. This guaranteed that the sampling sites were independent.

All deformations were performed freehand, similar to standard diagnostic sonographic scans, while imaging thrombus-containing veins at an in-phase and quadrature (IQ) data-capturing rate of 34 frames per second. All deformations were performed by one of the authors (J.M.R. or W.F.W.). Typically, each scan lasted 6 seconds, and about 1 cm of surface displacement was achieved. Surface displacements were estimated by speckle tracking. In-phase and quadrature data were subsequently transferred from the scanner to a personal computer for offline processing. After visual inspection of the stability of the speckle pattern from deformation movies, one scan with the best quality was identified to represent the patient. Best quality was defined as the segment with the highest correlation coefficient during tracking. Speckle cross-correlation is the method used for tracking motion in strain imaging (see below). The highest speckle tracking cross-correlation coefficient is an objective measure that defines which image has the best tracking and thus is independent of the individual performing the study or processing the data.

Signal Processing

We applied a phase-sensitive correlation-based 2-dimensional (2D) speckle-tracking algorithm to determine the in-plane frame-to-frame displacement.[25] The size of the cross-correlation kernel was 1.25 mm laterally × 0.4 mm axially.

Initial 2D displacements were estimated at the integer lags where the magnitude of the normalized correlation coefficient (ranging between 0 and 1) of the baseband signal is maximal. Furthermore, lateral displacement at subpixel accuracy was derived from a 2D second-order polynomial function that was the linear least square fit of the continuous surface description of the correlation coefficient. Following refinement of the lateral displacement, the phase 0-crossing position of the 2D analytic correlation function at the new lateral displacement was estimated as the final axial displacement. Before displacement estimation, normalized cross-correlation functions were spatially low-pass filtered to reduce the possibility of peak hopping. To improve the signal-to-noise ratio, incremental frame-to-frame displacements were accumulated referenced to the original geometry. Finally, axial strain was derived as the 1-dimensional spatial derivative of the axial displacement with respect to the axial direction.

To account for variability in the deformation force, strain must be normalized. Our current deformation system does not incorporate force measurements, so thrombus internal strains were normalized to the average strain (ie, total deformation) between the skin surface and the back wall of the vein (ie, total displacement of the transducer relative to the vein divided by the distance between the transducer and vein). After normalization, the 2D average was performed within the thrombus, and the resulting magnitude was used as the indicator of thrombus hardness.

Because strain analyses could not be performed in real time, certain examinations had to be retrospectively excluded from analysis on the basis of small deformations. If the overall deformation is small, there is no way to guarantee that the force has been transmitted to the thrombus. Hence, if the total deformation was less than 1%, the study was excluded from analysis.

Thrombus Echogenicity

To compare the echogenicity of acute and chronic thrombi, we selected the regions in the identified thrombi that had been used for strain estimation. We produced a mask over the thrombus and estimated the magnitude of the IQ signal inside the thrombus. We took the echogenicity of each thrombus as the average magnitude of the IQ signal in a thrombus measured at the initial position in the deformation sequence. This corresponds most closely to the appearance of the thrombus during standard imaging. To compensate for body habitus and other variables of scanning, we normalized the thrombus echogenicity measurements by the echogenicity of the neighboring arterial lumen at the corresponding frame used to estimate the thrombus echogenicities. The echogenicity of the arterial lumen was defined in the same way as the thrombus echogenicity, that is, the average magnitude of the IQ signal in the arterial lumen.

Statistical Analysis

The normalized strain magnitudes and relative thrombus-to-arterial lumen echogenicities between the two groups of patients were compared by the nonparametric Mann-Whitney *U* test. Data are presented as the median value and the interquartile range (IQR), the range between the 25th and 75th percentiles. The difference was considered statistically significant at $P < .05$. The two population distributions of the patients with acute and chronic DVT based on mean normalized strain magnitudes and relative thrombus-to-arterial lumen echogenicities were also compared via receiver operating characteristic (ROC) analysis (ROCKIT program; University of Chicago, Chicago, IL; available at: http://xray.bsd.uchicago.edu/krl/index.htm). The areas under the two ROC curves were compared by the method described by Hanley and McNeil.[26]

Results

On the basis of evaluations of the deformations, 3 initial studies in patients with acute DVT were excluded because of small deformations, leaving 23 cases for evaluation. Of the chronic cases, 5 studies had total deformations of less than 1%, leaving 23 cases that were included. We made echogenicity estimates in this same population.

Using all cases with total deformations greater than 1%, the median normalized strain magnitude for acute cases was 2.78 (IQR, 2.4–3.71), whereas the median normalized strain magnitude for chronic patients was 0.94 (IQR, 0.48–1.36). The difference between populations was highly significant ($P < 10^{-7}$). The distribution of these cases is shown in Figure 1. The average age of acute thrombi was 5.7 days, whereas all the chronic thrombi were older than 8 months.

For comparison, the distributions of the measured relative echogenicities between the thrombus and adjacent arterial lumen in the acute and chronic DVT populations are shown in Figure 2. The median relative echogenicity value for the acute thrombi was 1.4 (IQR, 1.17–1.54), whereas the median relative echogenicity value for the chronic thrombi was 4.5 (IQR, 2.5–7.5). The difference between the populations again was highly significant ($P < 10^{-5}$).

The derived ROC curves for normalized strain magnitude and relative echogenicities are shown in Figure 3. The area under the curve representing normalized strain magnitude is 0.97 ± 0.02 (SE). If one arbitrarily selects a value of 2 as a threshold for the normalized strain, the sensitivity for detecting an acute DVT is 87% with specificity of 91%. Because it is important to identify all acute thrombi for purposes of therapy, dropping the normalized strain threshold to 1.5 would produce sensitivity of 100% with specificity of 78%.

The derived ROC curve for relative echogenicity is shown in comparison with the curve for elasticity imaging (Figure 3). The area under the curve is 0.92 ± 0.04. The areas under the two curves were not significantly different ($P > .05$). To obtain 100% sensitivity for detecting an acute thrombus using echogenicity, specificity would be 74%. Typical examples of the normalized strain magnitudes and relative echogenicities between thrombi and the adjacent arterial lumen in an acute and a chronic DVT are shown in Figures 4 and 5.

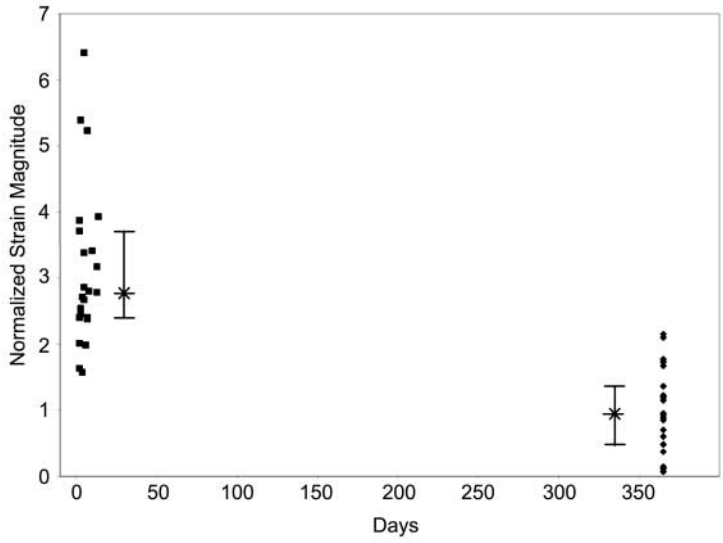
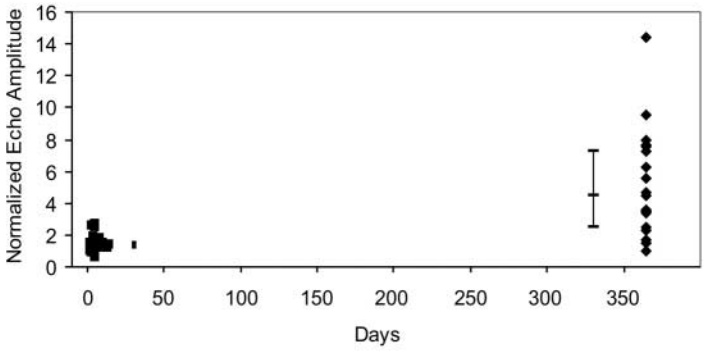


Figure 1. Distribution of average strains in the thrombi. Squares represent average normalized strain magnitudes in patients with acute thrombi. Diamonds represent patients with chronic thrombi and for convenience are placed at 365 days. The youngest of these thrombi is at least 8 months old, whereas all of the others are 1 year or older. The error bars to the right of the acute thrombi distribution and to the left of the chronic thrombi distribution represent the median values (marked with an x) and the 25th and 75th quartile values, respectively.

Figure 2. Distributions of average echogenicities in the thrombi based on the relative backscattered ultrasound signal amplitude between the thrombus and the adjacent arterial lumen. Squares represent the mean normalized thrombus amplitude in patients with acute thrombi. Diamonds represent patients with chronic thrombi, which are again for convenience placed at 365 days. The error bars to the right of the acute thrombi distribution and to the left of the chronic thrombi distribution represent the median value (central horizontal line) and the 25th and 75th quartile values, respectively (outer horizontal lines). Because the outer quartile values in the acute population are so close to the median for the acute distribution, we could not insert an x to mark the median value for the acute distribution. We, therefore, did not mark the medians with an x in this figure.



Discussion

Discriminating between acute and chronic DVT is an important medical problem. The treatment of DVT depends on the acuteness of the thrombus, with acute DVTs being treated with low-molecular-weight heparin or standard heparin, whereas symptomatic patients with chronic DVT generally have post-thrombotic syndrome and hence do not require anticoagulant therapy unless a new acute thrombus is detected.[12]

However, the distinction between acute and chronic DVT has been problematic for duplex sonography. This is particularly true in patients who have had a prior treated DVT and then subsequently have symptoms of a new DVT.[8,15] This is because, although duplex sonography is very good at detecting DVTs in the legs, the examina-

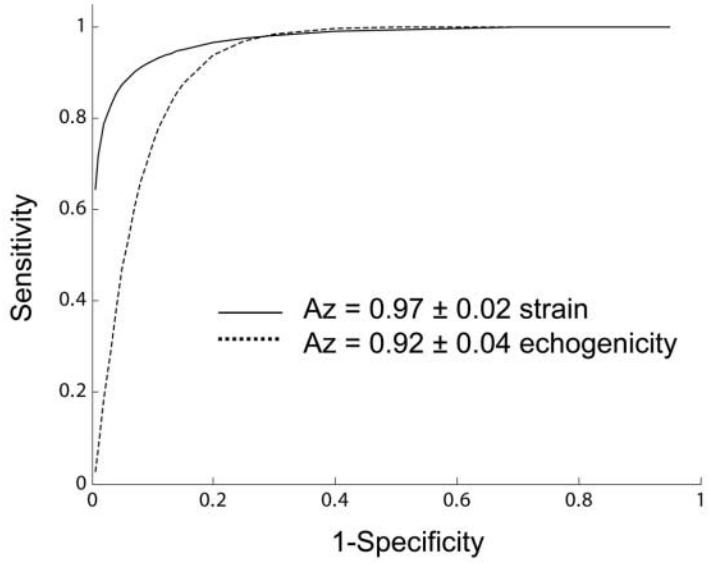
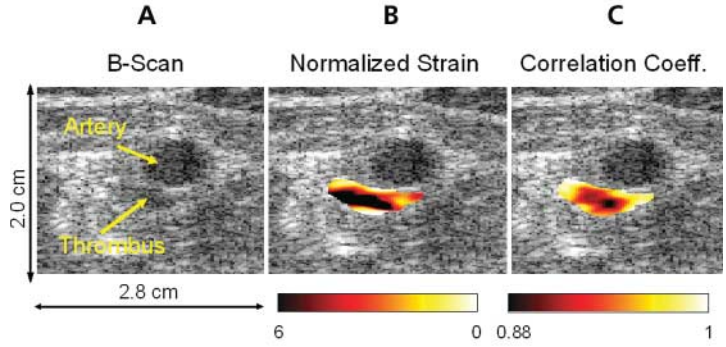


Figure 3. Receiver operating characteristic curves of the average normalized strain magnitudes and the average normalized echo amplitudes for the 46 patients, 23 with acute DVTs and 23 with chronic DVTs. The ROC curves were generated with the ROCKIT program from the University of Chicago. A_z is the area under each curve. The solid curve represents the sonographic elasticity measurements; the dotted curve represents the relative backscattered amplitude measurements. The difference between the two A_z values is not significant ($P > .05$).

Figure 4. Seven-day-old right femoral vein thrombus in a 77-year-old female patient. **A**, B-scan showing the gray scale image of the thrombus. The echogenicity of this thrombus based on normalized mean echo amplitude is 1.42. **B**, Normalized strain magnitude distribution in this thrombus. The color in each pixel in the thrombus represents the magnitude of the strain at that point divided by the average strain between the skin surface and the back wall of the vein. (This average strain corresponds to the total displacement between the transducer and the vein during a push divided by the original distance between the transducer and the vein.) The higher the strain magnitude, the softer the region. **C**, Magnitude of the average correlation coefficient (total range, 0–1) distribution for the positions in the thrombus over a limited display dynamic range of 0.88 to 1.0. The correlation coefficients represent the accuracy of tracking for each position. Because softer areas deform more, the correlation coefficients are typically lower than for hard areas. However, all the correlation coefficients are greater than 0.88, so tracking accuracy was excellent. The normalized average strain in this thrombus was 5.23.



tion has problems differentiating thrombi of different ages. Consequently, clinicians have had to resort to secondary criteria in attempting to determine the age of DVTs with duplex sonography. They include the size of the vein, the status of collaterals, and echogenicity of thrombi. Although there are disputes as to the efficacy of each of these parameters, none have proven sufficiently reliable to absolutely distinguish an acute thrombus in the presence of a chronic thrombus in all cases.[8–10,15,27–29] With regard to echogenicity, this is at least partly because of the relatively low dynamic range in echogenicity among thrombi for different ages.[27]

However, it is well accepted that thrombi harden as they age; therefore, sonographic elasticity imaging, which measures the hardness of tissue, should be able to determine DVT age. Recent work in animals has shown quite convincingly that this is the case.[16,17,20,21] Hence, there is very strong evidence that elasticity imaging estimates of DVT hardness should be a good way to estimate the age of DVT.

Furthermore, sonographic elasticity imaging has features that make it very attractive for determining the age of DVT, including the fact that the method requires that tissue be deformed, typically by pushing. This is totally consistent with duplex venous sonography, which also requires a push to diagnose DVT. Thus, final implementation of sonographic elasticity imaging would incorporate this technique directly into the standard duplex study so that thrombi would be diagnosed and aged simultaneously.

Our results strongly suggest that sonographic elasticity imaging can determine the age of DVT, and in this population, elasticity imaging performed at least as well as thrombus echogenicity. Statistical analysis showed that normalized strain magnitudes are highly significantly different between our acute and chronic DVT populations. Second, ROC analysis showed that the acute and chronic DVT populations were extremely well separated with the use of sonographic elasticity imaging given that the area under the curve was greater than 0.90. Differences of this magnitude should make it possible to determine the presence of acute thrombi in the presence of chronic thrombi, and elasticity imaging can, at least, be used in conjunction with other parameters such as echogenicity to determine the age of DVTs. As shown in Figures 4 and 5, the relatively soft center of the acute thrombus appears very different

from the uniformly hard chronic DVT on the basis of strain imaging.

We do recognize that our two populations were widely separated in their ages, so that the exceptional performance of elasticity imaging in our study may be modulated somewhat when, for instance, one tries to distinguish acute from chronic thrombi that are closer in age. This would also help explain the exceptional performance for relative echogenicity in our population. However, our model seems sufficient, at least for the circumstance in which an acute thrombus develops in a patient with post-thrombotic syndrome in whom a prior DVT may still be present. Hence, if an acute thrombus has questionably formed in conjunction with a chronic thrombus in such a patient, and the findings of increased echogenicity in the prior thrombus are in question, it is very possible that there will be a considerable difference in the measured elasticity between the supposed chronic thrombus and the fresh acute thrombus. Thus, elasticity imaging can add vital additional information under potentially difficult diagnostic circumstances. Furthermore, on the basis of animal studies, there is good reason to believe that elasticity imaging will be able to discriminate between thrombi much closer in age.[16,17,21] This will require further research, however.

One limitation of this study was that we had to do the processing off-line to produce strain images. Because of this, our analyses were obviously not performed in real time. However, this problem is not fundamental, and it will soon be possible to obtain strain images in real time.[30] Real-time elasticity imaging would not only greatly increase the speed of acquisition but also allow the user to detect those circumstances in which the applied deformation of a thrombus is too small or decorrelation is substantial because of out-plane motion. The operator could immediately repeat the deformation in these cases. Hence, small deformations in the examinations that we had to exclude from analysis would be immediately detectable during a standard duplex examination.

Finally, the DVT distributions between acute and chronic populations differed considerably. Nine of 26 acute DVTs were calf vein thrombi, but only 1 of 28 chronic DVTs was a calf vein thrombus. This difference was due to our chronic DVT population being composed mainly of patients having Greenfield filter follow-up examinations. Greenfield filters are typically not used in patients with only calf vein thrombi.

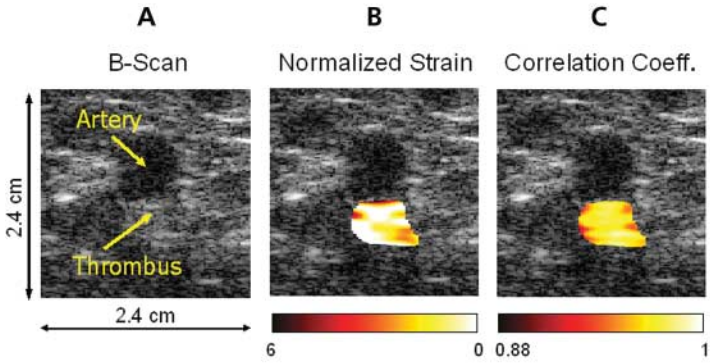


Figure 5. Chronic DVT of greater than 1 year of age in the right femoral vein in a 61-year-old male patient. **A**, B-scan with the thrombus deep to the artery. The echogenicity of the thrombus based on normalized mean echo amplitude is 4.4. **B**, Normalized strain magnitudes within the thrombus just as in Figure 4B. Notice that the thrombus is hard, that is, lower internal strain magnitudes, and it is more uniform than the acute DVT shown in Figure 4. **C**, The local correlation coefficients are uniformly high, greater than 0.88, showing that tracking is excellent. The average normalized strain magnitude in this thrombus is 0.14.

Multiple direct histologic studies of thrombi by Sevitt,[31–35] however, have shown no pathologic or structural differences associated with thrombus location. Hence, if a thrombus is detected, the mechanical properties of thigh, popliteal, and calf vein thrombi should be identical. Given that, we seriously doubt that this population difference influenced our results.

In conclusion, sonographic elasticity imaging can discriminate between acute and chronic thrombi, and in our population, it performed at least as well as echogenicity in this regard. On the basis of this finding, elasticity imaging can presumably be used to help differentiate an acute thrombus that has occurred in conjunction with an already present chronic thrombus. Although clearly suggested in animal studies,[16,17,21] the ability of elasticity imaging to distinguish between acute and chronic thrombi that are closer in age will require further study.

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