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Fluid flow in tumescent subcutaneous tissue observed with 3D scanning: massage accelerates injection dispersal

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Short title: Methods for measuring tumescent injections

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Abstract

Objective: Tumescent injections are used for regional anesthesia, lipoplasty, and antibiotic delivery amongst others. We evaluate the potential of 3D scanning to monitor the extent and dispersal of tumescent injections and compare it to a method based on CT. We use the scanning technique to determine whether massage and/or transcutaneous ultrasound accelerates the dispersal of the tumescent fluid.

Methods: 10-20 mL tumescent injections into live pig subcutaneous tissue were monitored with 3D scanning or CT and their response to waiting, massaging, or applying therapeutic ultrasound at

1 MHz and 3 W cm^{-2} was quantified. In a separate experiment, antibiotic was added to the tumescent fluid and serial blood samples were taken to monitor serum antibiotic concentrations. Massage or ultrasound was applied to generate a change in serum levels.

Results: Massage significantly accelerates dispersal when compared to waiting ($p < 0.05$). Simultaneous application of ultrasound does not accelerate dispersal further. No change in serum antibiotic levels could be detected in response to massage or ultrasound.

Conclusion: 3D scanning is an effective and inexpensive method of monitoring tumescent injections through the swollen skin profile. Although 3D scans do not capture the subcutaneous information revealed by CT, they do not require radiation or dedicated facilities.

Keywords: Tumescent Injection, 3D scanning, CT, Massage, Ultrasound, Fluid Dispersal

Introduction

Microcirculation in subcutaneous tissue is driven by the combination of hydrostatic and oncotic pressure gradients [1]. Fluid flows out of arterial capillaries, through the interstitial matrix, and into either venous capillaries or lymphatics. When fluids such as insulin, antibiotics, and vaccines are injected into the subcutaneous tissue, the incoming fluid exerts a pressure on the extracellular matrix that forces it to deform and stretch locally to accommodate the extra volume [2]. The infused fluid spreads locally by flowing through the matrix and systemically by absorption by venous capillaries or lymphatics. The usual microcirculation is temporarily disrupted until the injection has been fully dispersed and the matrix and fluid pressure return to their normal states.

Dispersal and absorption timescales are affected by many variables including injection volume, local tissue properties, temperature, motion of the patient, and whether the site has been massaged [3, 4]. Physical therapy clinics have used therapeutic ultrasound to reduce swelling for decades [5, 6], although the scientific basis for this procedure is questionable [7, 8].

To study the basic science of fluid flow in tumescent tissue it is essential to have a means of measuring the dispersal of tumescent fluids. The goal of this paper is to present a non-invasive technique based on 3D imaging to do just this. As a first application we study the relative effects of massage

and ultrasound on fluid dispersal in the subcutaneous tissue of healthy, live, juvenile pigs. We find that massage is effective at fluid dispersal, and simultaneous application of therapeutic ultrasound does not provide an additional effect. We further compare our 3D scanning technique to other methods of tracking tumescent fluid based on computed tomography (CT) and serial blood serum sampling.

Materials and Methods

We first describe preliminary measurements that informed our test protocol. 20 mL physiological saline was infused into subcutaneous tissue in three locations on the side of an anesthetized, juvenile Yucatán pig, and we observed the dissipation of the tumescence in response to waiting, massaging, or applying ultrasound (sonicating). The use of all animals in this study was approved by the UCLA Animal Research Committee (institutional review board no. 2014-142-02E) in accordance with accepted national standards and guidelines. High power “therapeutic ultrasound” operating at 1 MHz and 3 W cm^{-2} was applied with a Mettler Silberg Tissue Preparation System ME800 and ME8010 ultrasound handle (Mettler Electronics Corp., Anaheim, CA, USA) to one spot for two minutes. This “sonicated” spot should be thought of as a “sonicated and massaged” spot because the application of ultrasound requires moving the ultrasound handle while it is in contact with the skin with at least moderate pressure. Too light pressure results in a mismatch of acoustic impedance and the machine shuts itself off until contact is restored. We applied a force of about 10 N, which was distributed over the 14 cm^2 surface area of the circular and flat transducer head. We refer to “sonicated and massaged” spots simply as “sonicated” spots throughout the article, with massage being implied, to avoid unnecessary verbiage. To see the effects of massage alone, a second spot was massaged with a second, unpowered ultrasound handle at the same pressure for the same duration of time. The third spot was left untouched to observe the dissipation due to unaided spreading within the tissue.

Figure 1 shows photographs of the spots before and after the tests. A few conclusions can immediately be drawn. First, the initial shapes of the spots are different, suggesting that variations in subcutaneous tissue spot-to-spot might play a role, as is the case for insulin injections [9]. Second, the control spot (waiting) spreads on these timescales. We observe it changing

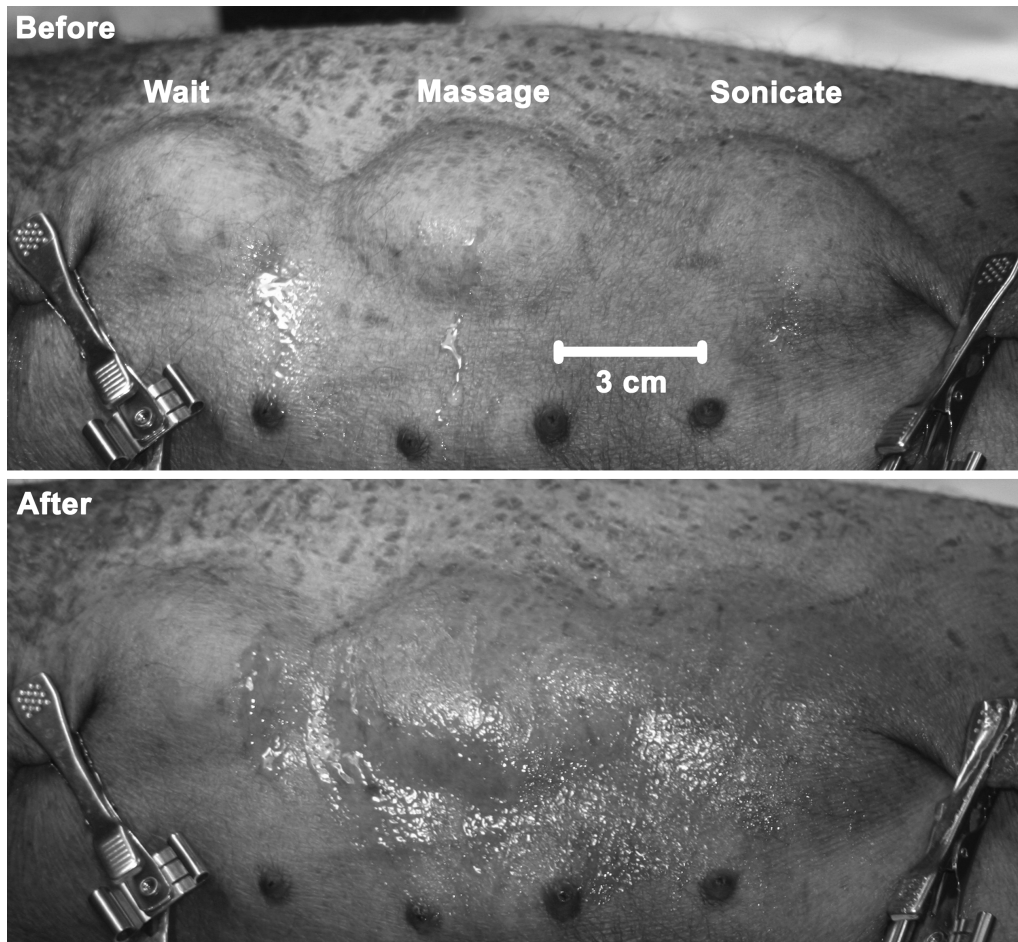


Figure 1: Three 20 mL tumescent injections in the side of an anesthetized pig. Spots are shown before (top) and after (bottom) either waiting, massaging, or sonicating for two minutes. Injections were performed in rapid succession, with the control (waiting) spot first, then the massaged spot, and finally the sonicated spot.

shape rapidly initially, but changes become imperceptible after about 5 min. Third, both the massaged and sonicated spots spread noticeably more than the control. Finally, there was no obvious difference in spreading between the massaged and sonicated spots. It is clear that to properly compare the effects of massage and sonication, we must 1) have a reliable method of measuring the tumescence height, 2) control for dead time between measurements, and 3) minimize variation in subcutaneous tissue as much as is reasonably possible.

A Scannify 3D scanner (Fuel3D, Greenville, NC, USA) was used to capture the tumescent skin profile. The scanner takes standard 2D images of the skin surface from two angles and three flash positions within 0.1 s, and reconstructs the 3-dimensional surface with a proprietary, cloud-based algorithm, to a manufacturer-specified resolution of $350\text{ }\mu\text{m}$. A tripod held the scanner about 15 in away from the region-of-interest. We shaved the pig to avoid complications with the scanner detecting the fur, and placed 3D markers (CT-SPOT #120, 4 mm diameter pellet colored black with a marker, Beekley Medical, Bristol, CT, USA) on the skin surface a few inches from the injection location to facilitate aligning the scans in post-processing. Scans were taken at the moment of maximal exhalation to reduce fluctuations from the pig's breathing.

Injection locations were chosen based on the thickness of subcutaneous tissue as judged by manual prodding, with preference given to thicker locations. Injection locations were always used in contralateral pairs to reduce variation in subcutaneous tissue. A control measurement (wait or massage) was performed on one side of the pig, and the test (massage or sonicate) at the symmetrically opposite location. We followed a strict timing protocol to account for the unaided spreading. A 3D scan was taken before any injection, defined to be at $t = 0$. The injection was performed as smoothly and uniformly as possible during the $t = 20 - 40\text{ s}$ time interval. A second scan was taken at $t = 50\text{ s}$. Beginning at $t = 60\text{ s}$, the test (wait, massage, or sonicate) was administered for 2 min. Sonication was at 1 MHz , 3 W cm^{-2} , with the Mettler device described above. Massage was performed with the ultrasound handle disconnected from the power supply, with the same motion and pressure as sonication. Ultrasound gel was used during both sonication and massage, but not for waiting. Between $t = 3$ and 3.5 min , the ultrasound gel was wiped from the skin (if present), and a third, final scan was taken at $t = 3.5\text{ min}$. This procedure was repeated for 20 injections over three pigs. Three pair were used to compare waiting and massaging, three to compare

Spot	Pig	Vol. [mL]	Region	Side	Test	ΔH_i [mm]	ΔH_f [mm]	r
1	2	20	Rump	Left	Wait	10.7	7.0	0.66
1	2	20	Rump	Right	Massage	10.1	3.6	0.36
2	3	20	Rump	Left	Wait	9.9	7.0	0.71
2	3	20	Rump	Right	Sonicate	11.6	5.7	0.49
3	1	10	Low Ab.	Left	Wait	9.7	6.5	0.67
3	1	10	Low Ab.	Right	Sonicate	9.1	3.3	0.36
4	2	20	Low Ab.	Right	Massage	8.3	4.0	0.49
4	2	20	Low Ab.	Left	Sonicate	10.3	5.3	0.51
5	3	20	Low Ab.	Right	Massage	10.6	7.3	0.69
5	3	20	Low Ab.	Left	Sonicate	10.7	7.4	0.69
6	2	20	Mid Ab.	Left	Massage	8.6	3.2	0.38
6	2	20	Mid Ab.	Right	Sonicate	8.8	3.0	0.34
7	3	20	Mid Ab.	Left	Massage	10.3	5.6	0.54
7	3	20	Mid Ab.	Right	Sonicate	11.4	6.7	0.59
8	1	10	Up. Arm	Left	Wait	10.2	7.1	0.69
8	1	10	Up. Arm	Right	Massage	12.5	6.5	0.52
9	2	20	Up. Arm	Right	Wait	8.9	7.6	0.85
9	2	20	Up. Arm	Left	Sonicate	10.3	6.3	0.62
10	3	20	Up. Arm	Right	Wait	9.8	9.5	0.97
10	3	20	Up. Arm	Left	Massage	9.8	6.2	0.63

Table 1: Description of tumescent injection locations, and change in tumescent heights in response to waiting, massaging, or sonicating. ΔH_i , and ΔH_f are the initial and final tumescence heights respectively. The dissipation ratio $r = \Delta H_f / \Delta H_i$ measures the drop in tumescence height in response to the test.

waiting and sonicating, and four to compare massaging and sonicating, as listed in table 1.

In addition to 3D scanning, we performed two complementary experiments, one with CT and the other with blood serum sampling, for comparison. CT scans were done at the UCLA Translational Research Imaging Center with a Somatom Definition 64 Dual Source Scanner (Siemens, Munich, Germany). An anesthetized adult Yucatán pig was placed in the scanner in a supine position. To minimize variation in subcutaneous tissue, we chose two spots on contralateral sides of the pig’s abdomen, and injected 20 mL saline containing 23 mg mL⁻¹ iodine contrast (3 mL Omnipaque 350 diluted to 45 mL) into each. The first spot injected was left to evolve unaided (control). Ultrasound was applied to the other spot with the Mettler device for 1 min at 3 W cm⁻², and then massaged for 1 min with the same ultrasound handle and pressure. CT scans were taken immediately after injection, after sonicating, and after massaging.

Serum sampling can measure the effect of massage and ultrasound on the uptake of tumescent fluid by the circulation directly. Our procedure is described in detail in [10]. Briefly, 20 mL of water with 25 mg kg⁻¹ cefazolin was injected tumescently into subcutaneous tissue of the right flank of three anesthetized juvenile Yucatán pigs. A left femoral arterial catheter was placed under direct visualization via cut-down. Blood samples of 3 mL were taken every 5-10 min over 2-3 hr. The tumescence in the first pig (6.5 kg) was left alone to be absorbed unaided (control). In the second pig (6.5 kg), 1 MHz therapeutic ultrasound was applied at 3 W cm⁻² for 1 min each, at 32, 90, and 147 min after the injection. In the third pig (11.5 kg), the tumescence was massaged with the ultrasound handle, at the same pressure as with ultrasound application, at the same times after injection, for 1 min each. The blood samples were centrifuged at 2200×g for 10 min, and refrigerated at -80 °C until shipping on dry ice to Hartford Hospital for the assay. Cefazolin assay was performed at the Center for Anti-Infective Research and Development at Hartford Hospital using a validated high performance liquid chromatography method similar to that reported in [11].

Analysis and Results

3D scan analysis and post-processing proceeded as follows: We 3D cropped each scan to contain only a region a few inches larger than the tumescence

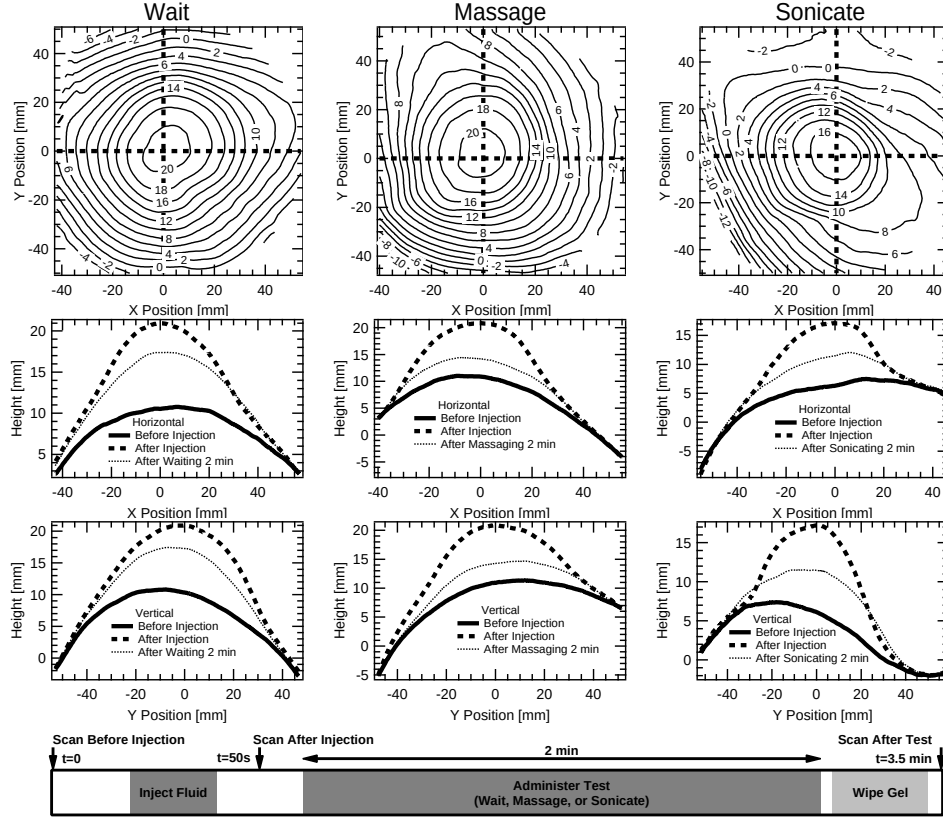


Figure 2: Contour plots of three example tumescent skin profiles immediately after injection (top). Lineouts of the skin profile in the $Y=0$ and $X=0$ planes display the change in tumescence shape in response to waiting, massaging, or sonicating. Experimental timeline is shown along the bottom of the figure.

using the Fuel3D Studio software that came with the scanner, and exported a list of X, Y, Z coordinates laying on the pig-skin surface. A Python script read in the coordinate lists of each scan, and aligned the three scans of each spot by minimizing the difference between the edges of the scans where the tumescence did not effect the skin profile. After alignment, the coordinate system was rotated so that the tumescence rose along the Z direction, with the direction of the X and Y axes chosen arbitrarily. We verified proper alignment by taking lineouts of the skin profiles along the edges of the scans and checking that they overlapped.

Figure 2 (top) shows contour plots of the tumescent skin profile immedi-

Massage vs Wait

Spot	r_w	r_m	f_{mw}
1	0.66	0.36	0.46
8	0.69	0.52	0.24
10	0.97	0.63	0.35
Average f_{mw}			0.35 ± 0.06

Sonicate vs Wait

Spot	r_w	r_s	f_{sw}
2	0.71	0.49	0.30
3	0.67	0.36	0.46
9	0.85	0.62	0.28
Average f_{sw}			0.35 ± 0.06

Sonicate vs Massage

Spot	r_m	r_s	f_{sm}
4	0.49	0.51	-.05
5	0.69	0.69	0
6	0.38	0.34	.09
7	0.54	0.59	-.09
Average f_{sm}			$-.01 \pm 0.04$

Table 2: Dissipation ratios and two-test-enhancement-factors for massage vs wait, sonicate vs wait, and sonicate vs massage. Displayed uncertainties are the standard deviation of the mean.

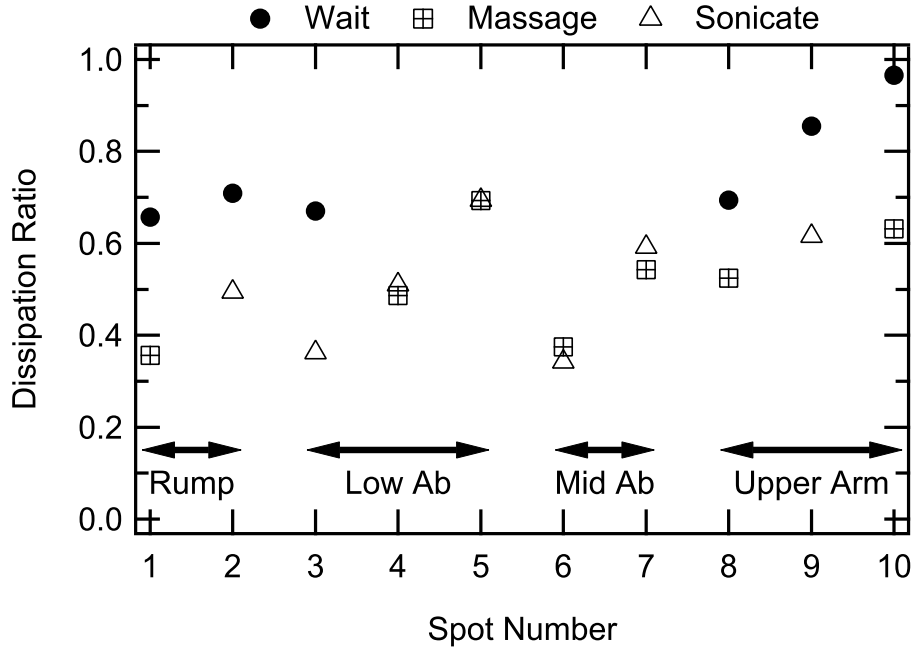


Figure 3: Dissipation of tumescent spots in response to waiting, massaging, or sonicating. A dissipation ratio of 1 means the tumescence height was unchanged, and a dissipation ratio of 0 means the tumescence was no longer observable. We ascribe more meaning to the difference in dissipation ratio between the two tests at contralateral spots than to differences between spots.

ately after injection for three example injections. Lineouts of the skin profile in the $X=0$ and $Y=0$ planes are shown in figure 2 (bottom) before and after injection, and after waiting, massaging or sonicating. We define the initial tumescence height, ΔH_i , as the maximum difference between the skin profiles before and after injection, and the final tumescence height, ΔH_f , as the maximum difference between the skin profiles before injection and after the test. Their ratio, $r_p = \Delta H_f / \Delta H_i$ is a measure of the effectiveness of the test at dispersing the tumescence that we call the “the dissipation ratio”. The index $p = w, m$, or s indicates the test performed and stands for waiting, massaging, or sonicating respectively. The dissipation ratio varies from 1 to 0 as the tumescence height drops. ΔH_i , ΔH_f , and the dissipation ratio are listed in table 1 for all 20 injections. In addition, the dissipation ratios are

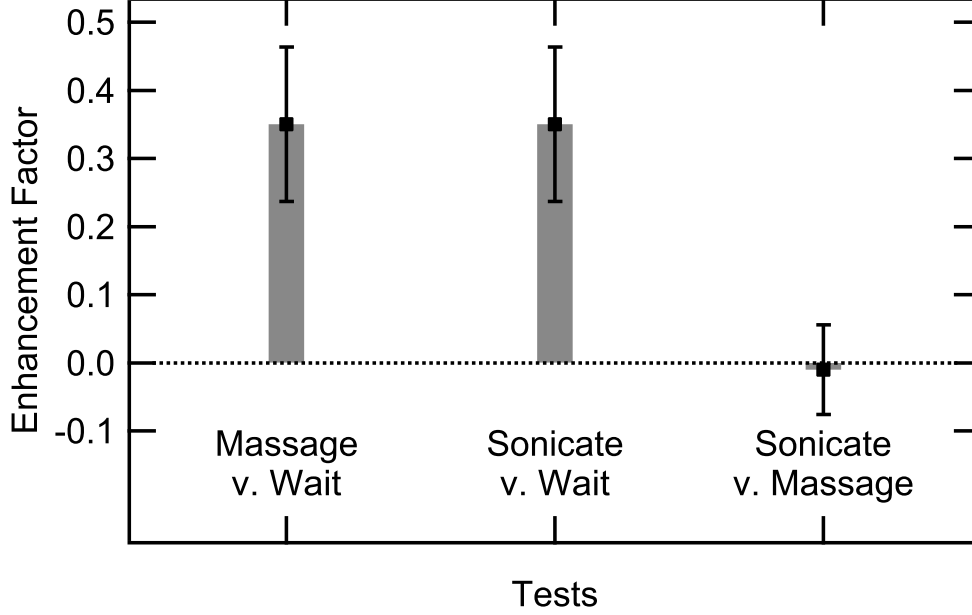


Figure 4: Two-test-enhancement-factors measuring the increase in tumescence dissipation between the two tests. Uncertainty bars indicate the 80% confidence interval.

shown graphically in figure 3.

While we could proceed by averaging the dissipation ratio of all spots with the same test (0.76 ± 0.05 , 0.52 ± 0.05 , 0.52 ± 0.05 , average $\pm$ standard deviation of the mean for waiting, massaging, and sonicating respectively), greater statistical significance is obtained by comparing tests at contralateral locations so that variations in tissue properties are reduced. We define the “two-test-enhancement-factor,” $f_{pq} = 1 - r_p/r_q$ as a measure of the enhanced dissipation due to test p compared to test q . f_{pq} varies between 0 and 1 and is 0 for no enhancement, and 1 for complete tumescence dispersal ($r_p \lesssim r_q$ by assumption). The two-test-enhancement-factors for massage vs wait, sonicate vs wait, and sonicate vs massage are listed in table 2, and are shown graphically in figure 4.

Results from the CT experiment are shown in figure 5. The top panel is an axial CT image taken immediately after injection, at the plane of maximum tumescence thickness. The tumescent volume attenuates x-rays more than

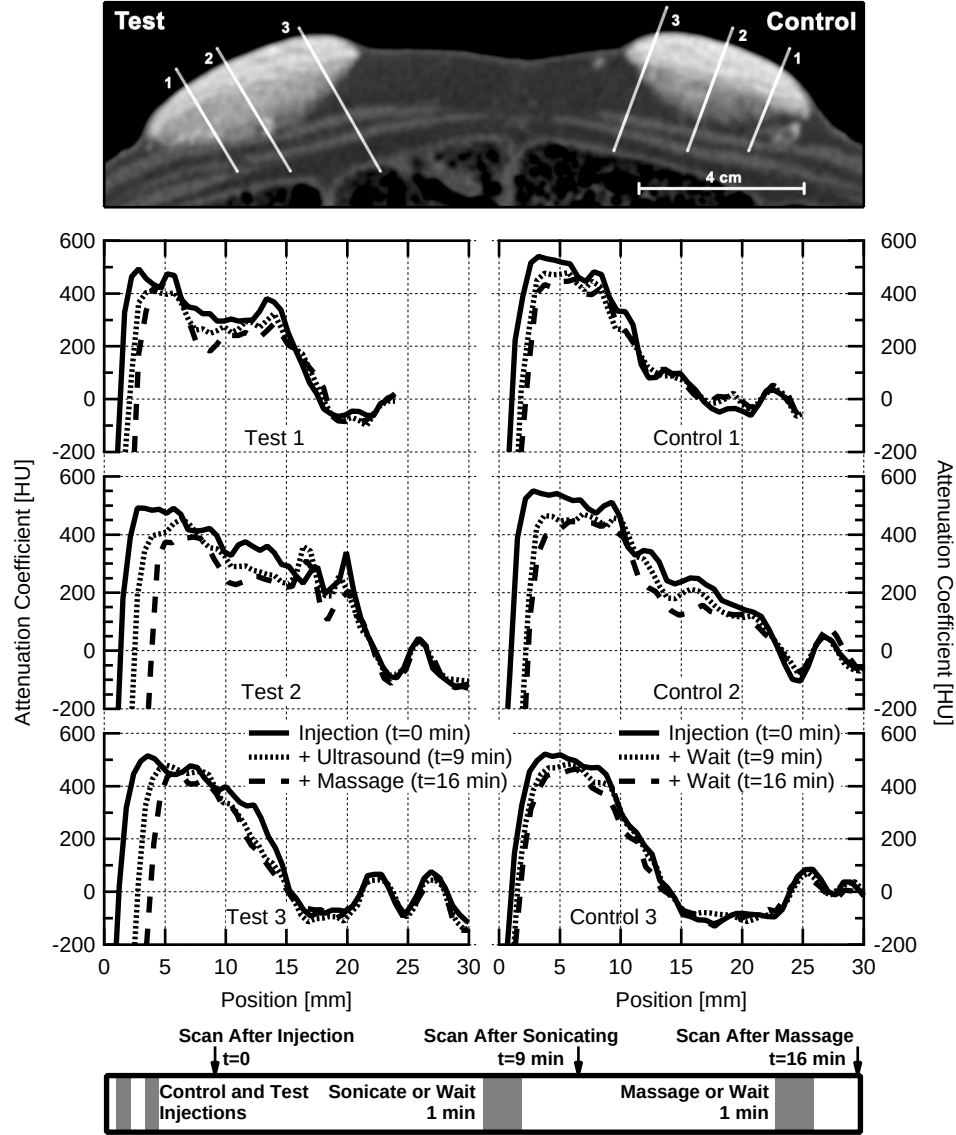


Figure 5: Axial CT image of two contralateral tumescent injections into pig abdominal subcutaneous tissue (top). One spot (control) was left untouched, to evolve on its own. The other (test) spot was first sonicated, and then massaged. Three lineouts crossing the tumescent regions, taken along the numbered white lines in the images, are shown below. Experimental timeline is shown along the bottom of the figure.

the surrounding tissue, thanks to the dilute contrast added to the fluid, and appears whiter in the image. Lineouts crossing the tumescent spots are displayed in figure 5 (bottom panels). In the empty space above the abdomen, the x-ray attenuation is negligible (large negative number), and shoots up to a few hundred where the lineout crosses the skin surface. The location of the skin surface is a measure of the tumescence dissipation, and is easily identified on the graphs. Proper alignment of the lineouts taken at different times is verified by checking the alignment of features 2-3 cm below the skin surface. Looking at the control curves, we see that the skin surface drops noticeably between $t=0$ and 9 min, but not between $t=9$ and 16 min. The test curves drop more than the control curves in both time periods, about equally after applying ultrasound or massage.

Data from the serum sampling experiments are shown in figure 6. A pharmacokinetic analysis is done in [10], here we focus on the modulation effects of massage and ultrasound. Depending on the mechanism of increased cefazolin absorption due to massage or ultrasound, we expect different changes in the serum cefazolin concentration curves. If ultrasound reversibly enhances capillary permeability, for instance, we expect a temporary increase in the derivative of the curve during ultrasonic application, that would appear as a spike in figure 6 (bottom). If massage spreads the tumescence, it effectively increases the capillary surface area in contact with the tumescence, and we expect an extended increase in the derivative of the curve, that would appear as a step in figure 6 (bottom). No consistent spike-like or step-like increase in the derivative of the plasma cefazolin curve is observed at the times of massage or ultrasound application.

Discussion

The 3D scanning and CT data are consistent with our preliminary visual observations. The massage-wait enhancement factor is numerically identical to the sonicate-wait enhancement factor, $f_{mw} \approx f_{sw} \approx 0.35 \pm 0.12$ (± 0.26), at 80% (95%) confidence levels obtained by multiplying the standard deviation of the mean by the appropriate Student's t value ($N=3$). Directly comparing massaging to sonicating gives the sonicate-massage enhancement factor, $f_{sm} \approx -0.01 \pm 0.06$ (± 0.12), and so we can say with 90% (97.5%) confidence that adding ultrasound to massage does not enhance dispersion by more than 6% (12%) ($N=4$). While more runs would improve our statistics

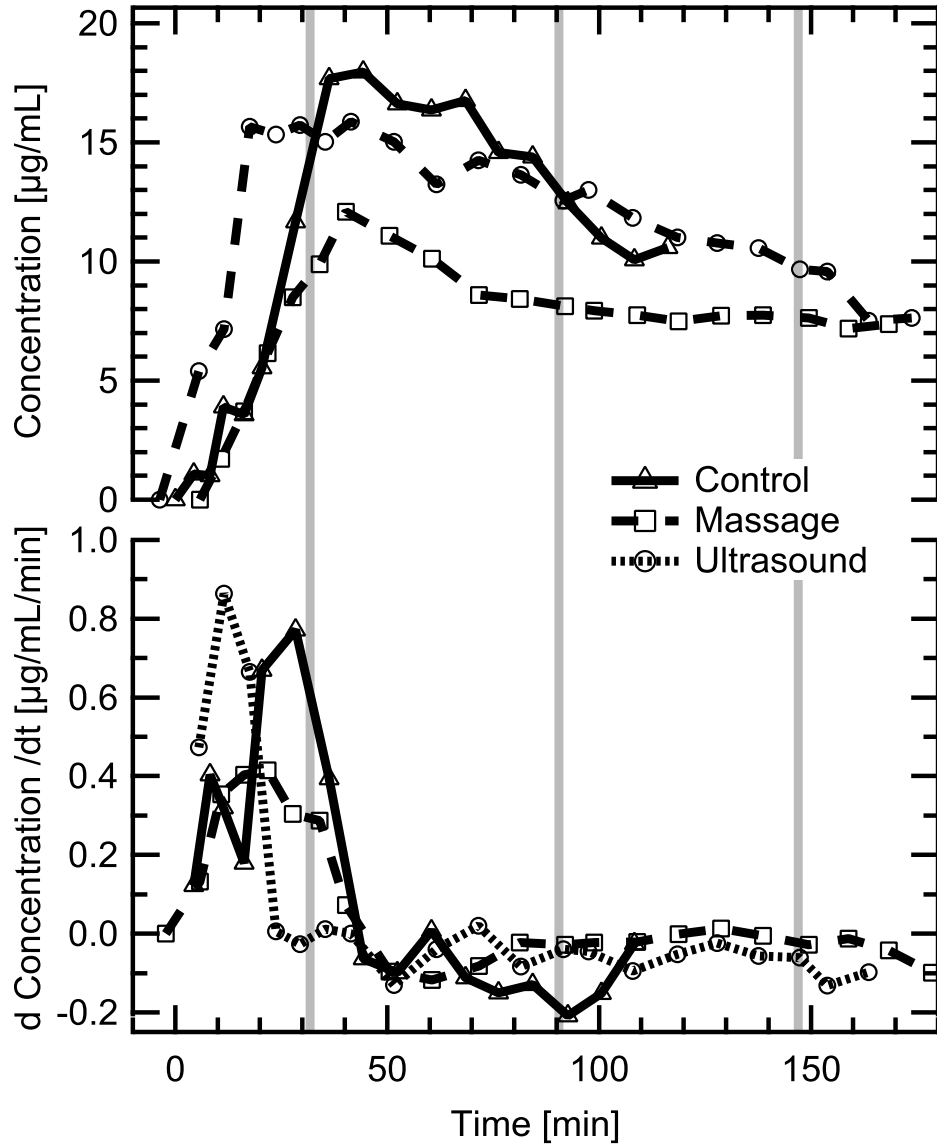


Figure 6: Plasma cefazolin concentration following a 20 mL, 25 mg kg⁻¹ tumescent injection into the flank of anesthetized pigs (top). Derivative of plasma cefazolin curves (bottom). Vertical gray lines in the figure indicate the times of massage or ultrasound application for 1 min each.

and narrow down the confidence intervals, we can conclude that massage is a potent means of dissipating tumescent fluid and its effect cannot be ignored when testing that of ultrasound. In fact, when considering ultrasound in the absence of massage, null results are the most likely conclusion.

The subcutaneous dispersal of fluid measured by CT also resolves a difference between waiting, massaging, and sonicating. By nature, this type of data contains far more information than the skin profile alone since it reveals the full 3D structure of the tumescent tissue beneath the skin. Our relatively simple approach of looking only at changes in the skin position in the CT images neglects the rich information contained in the full image. More sophisticated image analysis could yield a map of the degree of tissue expansion determined through the contrast agent density, for instance. If the change in skin height is the only variable of interest, 3D scanning is capable of achieving similar or better resolution than CT, without dedicated facilities, no radiation dose considerations, and less upfront cost (\$1-2k for a 3D scanner compared to \$75-2000k for a CT scanner).

Whereas 3D scanning responds to the swelling induced by an injection, CT measures the dispersal of the contrast agent. In principle, the contrast agent may or may not be carried along with the saline as it perfuses through subcutaneous tissue, depending on the relative size of the contrast agent and the interstitial pores [12]. Our CT results demonstrate that molecules about the size of the contrast agent or smaller are carried by the fluid. Since the atomic weight and size of the contrast agent [13] is comparable, but larger, than the size of a standard antibiotic such as cefazolin [14], we do not expect the perfusion properties to be very different. Therefore, we are confident that the fluid dispersal measured by 3D scanning amounts to a measurement of drug dispersal.

In an apparent contradiction, neither massage nor ultrasound had an obvious affect on the subcutaneous cefazolin pharmacokinetic curves. It is possible that in healthy tissue the tumescence had spread enough on its own in the 32 min before massage or ultrasound was administered that any additional spreading and absorption was negligible. Any increase in absorption rate was below our resolution. Another possibility is that massage and ultrasound only accelerate dispersal if applied shortly after the injection, during the rapid unaided spreading phase, when high pressure gradients exist. Follow up investigation will be needed to clarify these issues.

Perspectives

Time-resolved 3D scanning of tumescent injections provides a non-invasive way of observing and measuring fluid flow in interstitial tissue that can reveal underlying tissue properties that are otherwise difficult to obtain directly in a live system [15]. Clinics can use the technique to monitor the residence time of tumescent anesthesia [16] or antibiotics administered directly into wounds [17–20] or adjust flow rates in hypodermoclysis [21–23]. With the 3D scanning technique, we have shown with confidence that the physical therapy practice of applying therapeutic ultrasound for swelling dispersal is unjustified.

Conclusion

We have developed a non-invasive method using 3D photography that yields a time-resolved picture of the extent and dispersal of a tumescent injection. In this paper we have applied the technique to compare the effects of massage and therapeutic ultrasound to the dispersal of a tumescent injection in the subcutaneous tissue of healthy pigs. We find that massage and sonication (which also includes unavoidable massage) yield equivalent improvements over a control. Somewhat paradoxically, we find that serum levels of cefazolin are unaffected by massage and ultrasound relative to a control.

The spreading of fluid in the interstitial matrix is described by poroviscoelastic theory [2, 24]. Poroelasticity addresses the problem of fluid motion in a porous medium where the fluid shear exerts a force that deforms the medium, and strain in the medium causes pressure gradients that drive the fluid flow. Viscoelasticity addresses the relaxation of the polymers that constitute the interstitium, which have a time (or frequency) dependent elasticity. The combined poroviscoelastic response of the body is responsible for the rich dynamics displayed at the injection site as fluid moves away. Looking forward, the capability of 3D scanning to noninvasively capture the tumescent skin profile in both space and time will allow the measurement of tissue poroviscoelastic parameters in a live system and a better understanding of the interstitial matrix.

Acknowledgments

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