Changes of interstitial fluid volume in superficial tissues detected by a miniature ultrasound device

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Received 11 June 1999; accepted in final form 1 March 2000

Eichler, Wolfgang, Christine Eisenbeiss, Jan Schumacher, Stefan Klaus, Rolf Vogel, and Karl Friedrich Klotz. Provoked changes of interstitial fluid volume in superficial tissues detected by a miniature ultrasound device. J Appl Physiol 89: 359–363, 2000.—We evaluated the changes of tissue layer thickness in circumscribed superficial tissue areas with a 10-MHz A-mode and a 20-MHz B-mode ultrasound device under alterations in body posture and plasma volume to detect fluid shifts between the different compartments. In 20 male volunteers, we measured tissue thickness by A mode and corium and subcutis thickness by B mode at the forehead before and 30 min after three procedures: change from upright to supine position (P1); change from upright to 30° head-down-tilt position (P2); infusion of 10 ml/kg body wt of Ringer solution (P3). We found a significant correlation between baseline tissue thickness and the sum of corium and subcutis thicknesses ($r = 0.75$, $P < 0.01$). The changes of body posture and plasma volume resulted in significant increases of tissue thickness (P1, 2.9%; P2, 11.6%; P3, 5.8%) and corium thickness (P1, 4.7%; P2, 8.1%; P3, 9.1%) but not of the sum of chorium and subcutis thicknesses. We conclude that fluid shifts from the intravascular to the extravascular compartment are detectible by evaluating corium thickness with a B-mode, or more easily tissue thickness with an A-mode, ultrasound device.

pulmonary edema physiopathology; capillary permeability; hydrostatic pressure; heart failure; congestive complications

ANY CHANGE IN INTERSTITIAL fluid volume must result from an imbalance of net capillary filtration and lymph flow, as long as cell volume remains constant. After Starling's studies (14), it became generally accepted that the net flux through the capillary wall is determined by the sum of hydrostatic and protein osmotic pressure differences between capillary plasma and interstitial fluid and furthermore by the permeability of the capillary membrane.

Impairment in the Starling equation (for example, by increased capillary hydrostatic pressure, decreased plasma colloid osmotic pressure, or enlarged permeability) can lead to edema. For early recognition and to avoid the deleterious consequences of inadequate fluid administration, it was suggested to have information about this compartment (1, 5, 7, 15). The different branches of the cardiovascular system may be compared with a system of communicating tubes, so it can be hypothesized that volume shifts take place in similar ways in the low-pressure parts of the superficial tissues, in which they can be traced more easily, and in the deep tissues, such as in lungs or muscles (8).

Therefore, an objective and sensitive parameter measuring interstitial volume changes within the body shell is very desirable. The superficial tissue thickness can easily be determined by ultrasound techniques at body sites where the underlying bone provides a good backwall echo, such as the forehead or pretibial area. It has been shown that the peripheral tissue thickness will be influenced by infusion regimes, renal and cardiac performance, body posture, and heat exposure (8, 9). In the perioperative setting, the changes in tissue thickness by nil-by-mouth period, fluid replacement, and positioning are detectable by ultrasound (11, 12).

In the present study, we evaluated the changes in tissue thickness of small circumscribed superficial tissue areas with a miniature 10-MHz A-mode miniature ultrasound device under various experimental conditions with alterations in body posture and plasma volume. The aim of the study was to compare the handheld ultrasound device in vivo with a high-reso-
lution 20-MHz B-mode ultrasound device by simultaneous use. Furthermore, it had to be investigated in which compartment of the skin volume changes take place, and, finally, we set out to prove whether the observations made can be brought into agreement with what is already known about the low-pressure system.

METHODS

Experimental procedures. After obtaining ethics committee approval and written informed consent, we examined 20 healthy male volunteers, aged 24–37 (mean 29.2) yr, weighing 62–94 (mean 77.7) kg and having a normal body mass index. The subjects presented themselves normohydrated in the morning of investigation after a usual breakfast. Tissue thickness was measured in a thermoneutral environment by A-mode and immediately afterward by B-mode ultrasound; color images were saved for later evaluation. Three different procedures were performed, and the tissue thickness was evaluated before and 30 min after each procedure at a marked spot at the middle forehead. Between each procedure was a time interval of 30 min to regain the baseline conditions.

In procedure 1 (P1), the subjects were tilted from the upright into the supine position.

In procedure 2 (P2), the subjects were tilted from the upright into the 30° head-down-tilt position.

In procedure 3 (P3), 10 ml/kg body wt of Ringer solution were infused within 15 min. Hematocrit (Hct) was determined before and after infusion of Ringer solution.

Tissue thickness monitoring by A mode. Tissue thickness was determined at a marked spot at the middle forehead, avoiding the vicinity of large blood vessels, by taking the mean value of three measurements made by an A-mode ultrasonic pulse-echo device. The transducer probe transmits a brief ultrasound burst that propagates through tissues but not bone and is reflected back and received by the same probe (A mode). After the measurement, tissue thickness is displayed digitally. The device (weight 400 g) operates on a frequency of 10 MHz and has a range of 0.5–20.0 mm (GDM, Krautkrämer, Hürth, Germany). It is a newly designed version of a similar apparatus introduced by Kirsch and coworkers (8, 9) that meets the German safety standards and is now available for medical purposes. After the in situ analysis of intraobserver error, we found a standard deviation for the mean value of 0.048 mm (1%). The resolution is 0.5% of the values obtained in subjects (assuming an average tissue thickness of 4.6 mm) with a standard deviation of 1%. For interobserver error in two different observers, we found a correlation of \( r = 0.99 \) (P < 0.01, \( n = 20 \)), and the mean of differences amounted to 0.025 ± 0.02 mm. In the present study, the tissue thickness measurements were undertaken by a medical trainee who was not informed about the aim and background of the study. He was not aware either of the previous results of the A-mode device or of the corresponding results of the B-mode device.

Tissue thickness monitoring by B mode. To investigate the different layers of the skin and to validate the miniature A-mode device in vivo, we used a 20-MHz high-resolution B-mode scanner (Dermasonic C, Cortex Technology, Hadsun, Denmark). It enables the investigator to save images to hard disk and to evaluate the size of the corium and the subcutis up to a depth of 10 mm. The lateral resolution amounts to 200 \( \mu \)m and the axial resolution to 80 \( \mu \)m. Measurements by two observers in the same subject at a marked spot on the forehead resulted in a correlation of \( r = 0.98 \) (P < 0.01, \( n = 20 \)). The mean of differences amounted to 0.02 ± 0.03 mm.

For later evaluation, the saved images were blinded, and the tissue thickness of the corium and the subcutis were estimated by an experienced investigator. In normal skin, the corium is markedly echogenic and sharply demarcated from hypoechoic subcutaneous fat. Therefore, the distance between the transition of epidermis to corium and corium to subcutis, and the distance between the transition of corium to subcutis and bone were measured vertical to skin surface and with unchanged device adjustments. It has to be noted that the thickness of the epidermis is not determined correctly by this device because of impedance changes at the transition between the ultrasound probe and the skin surface (2).

Statistical analysis. All absolute values are presented as means ± SD; the relative changes are given as means ± SE. To evaluate the statistical significance of tissue thickness, chorium, subcutis, chorium plus subcutis, and Hct differences, we used the paired t-test after verifying normal distribution by the Kolmogorov-Smirnov test. \( P < 0.05 \) was considered significant.

RESULTS

Tissue thickness monitoring by A mode. In the upright position, the subjects presented before the procedures \( t_0 \) with a forehead tissue thickness between 3.7 and 5.4 mm, resulting in a mean tissue thickness of 4.47 ± 0.52 mm. After P1, tissue thickness increased up to 4.59 ± 0.52 mm (difference 0.13 ± 0.03 mm, ranging from −0.1 to 0.3 mm). After P2, tissue thickness increased to 4.99 ± 0.54 mm (difference 0.52 ± 0.05 mm, ranging from 0.3 to 0.9 mm). P3 resulted in an enlargement of tissue thickness up to 4.72 ± 0.46 mm (difference 0.26 ± 0.08 mm, ranging from −0.1 to 0.9 mm). All procedures led to significant changes compared with \( t_0 \) (P1–P3: \( P < 0.01 \)).

Chorium and subcutis thickness examination by B mode. Forehead corium thickness was measured 2.98 ± 0.47 mm at \( t_0 \) (range 2.3–4.1 mm). All procedures led to a significant increase of corium thickness compared with \( t_0 \) (P1 and P3: \( P < 0.05 \); P2: \( P < 0.01 \)) as follows: 0.14 ± 0.08 mm (P1), 0.24 ± 0.05 mm (P2), and 0.27 ± 0.1 mm (P3). Forehead subcutis thickness at \( t_0 \) was 1.05 ± 0.41 (range 0.41–1.78 mm). Subcutis thickness decreased by alteration of body posture (P1 and P2) and infusion therapy (P3); however, only P2 showed a weak significance (\( P = 0.014 \)). The sum of chorium and subcutis thicknesses should essentially coincide with tissue thickness. The mean sum at \( t_0 \) amounted to 4.03 ± 0.54 (range 2.95–4.87 mm) and was not altered significantly by P1–P3 compared with \( t_0 \). Fig. 1 demonstrates the differences of means in skin thickness detected by each method before and after each procedure.

Comparison of tissue thickness to the sum of chorium and subcutis thicknesses. In the primary determined values in upright position \( n = 20 \), the sum of corium and subcutis was compared with the tissue thickness values (Fig. 2A), and a significant correlation of \( r = 0.75 \) (\( P < 0.01 \)) was found. We intentionally chose only the primary results before procedure P1 to P3 to exclude dependent values in this evaluation. To compare both methods in measuring skin thickness, a Bland-
was used. From the differences of tissue thickness and chorium plus subcutis thickness, a bias of +0.48 mm with a standard deviation of ±0.46 mm was derived.

**Differences in Hct before and after P3.** During procedure P3 with infusion of 10 ml/kg body wt, the mean Hct decreases significantly from 46.5 ± 2.3% to 42.3 ± 2.02% (*P < 0.05, **P < 0.01; results of paired-samples *t*-test of respective mean of absolute values.

**DISCUSSION**

Clinically, edema may be detected at an expansion of interstitial fluid volume of 50–100%, but long before edema becomes apparent an interstitial edema-preventing mechanism is activated. It is reflected by automatic adjustments of the interstitial forces, namely, a rise in interstitial pressure or a drop in interstitial colloid osmotic pressure (3).

The connective tissues of the human skin are characterized by a low cell density and an abundance of extracellular macromolecular material and are regarded as the water stores of the body (3, 10). The combination of the large number of proteoglycan filaments and the entrapped fluid within gives connective tissue the characteristics of a tissue gel. It has been reported that these tissues hold about one-third of the total interstitial fluid (7).

Previous publications on the fluid distribution within superficial shell tissues have introduced a miniature ultrasound A-mode device as a promising possibility of monitoring hydration state (8, 9, 11, 12). The different branches of the cardiovascular system may be compared with a system of communicating tubes, so it can be hypothesized that volume shifts take place in similar ways in the low-pressure parts of the superficial tissues, where they can be more easily traced than in the deep tissues such as the lungs or the muscles (8).

A comparison of the absolute values obtained by the ultrasonic method with those of autopsy measure-
ments revealed a satisfactory agreement postmortem (8). Furthermore, the validity of the method was indirectly tested under various experimental conditions such as orthostasis, water immersion, heat exposure, and microgravity environment. The results were in accordance with what is already known about low-pressure systems (8, 9). Our data from previous studies showed the expected reduction of tissue thickness after a nil-by-mouth period and the expected increase after fluid replacement and head-down-tilt positioning, respectively, measured at the forehead (11, 12). These investigations in the perioperative setting revealed that ultrasound may prove useful for noninvasive assessment of fluid balance. Nevertheless the above-mentioned influences typically coexist during this setting, and it remained unclear in which layer of the skin volume changes take place.

Both investigated devices are able to determine the distance between skin surface and bone. Additionally, the high-resolution B-mode device allows differentiation between corium and subcutis. The thickness of the epidermis is not recorded because of impedance at the transition between ultrasound probe and skin surface; however, the average epidermis thickness on the forehead is specified at ~50 μm (16). Therefore, the sum of corium and subcutis thicknesses should correspond with tissue thickness minus epidermis thickness.

The mean values of tissue thickness, chorium thickness, subcutis thickness, and chorium plus subcutis thickness corresponded with results of previous studies concerning total skin thickness and their components (6, 13). The comparison of tissue thickness and the sum of chorium and subcutis thicknesses in vivo revealed a good correlation between both methods. Tissue thickness seemed to slightly overestimate the skin thickness compared with the sum of chorium and subcutis thicknesses by 0.48 mm. This is not sufficiently explained by the typical epidermis thickness reported by Whitton and Everall (16), which could not be evaluated by the B-mode device.

Changes of body posture and plasma volume served as two different ways to induce volume shifts into the tissues belonging to the shell of the body, in contrast to many earlier methods dealing with volume shifts within deep tissues such as the lung (5). During P1 and P2, the capillary hydrostatic pressures in the lower parts of the body may, whereas they rise in the upper parts like forehead area (7). P3 with increase of plasma volume indicated by a reduced Hct also means elevated net capillary filtration, and, in accordance with the Starling equation, that can result in augmentation of interstitial fluid with extended tissue thickness (3, 15). The time courses of the redistribution of body fluids during tilt-table experiments were already investigated by Kirsch and co-workers (8). They found rapid changes at the forehead within the first 5 s, and after 10 s the tissue thickness remained unchanged until the end of the tilt. Therefore, we considered an interval of 30 min between the procedures P1 to P3 as sufficient to reestablish baseline values. By contrast, the kinetics of fluid distribution after infusion are expected to be much slower and to be inaccurately predictable. Therefore the procedure with the augmentation of plasma volume (P3) was placed at the end.

The miniature A-mode ultrasound device reliably traced the expected enlargement of tissue thickness by both tilting maneuvers and infusion and thereby confirmed the results of our previous studies (11, 12). The B-mode ultrasound device allowed differentiation between corium and subcutis. P1–P3 led to a significant augmentation of the corium, whereby the subcutis tended to decrease. The overall distance of chorium plus subcutis did not lead to significant changes. Corium thickness also revealed the pattern of augmentation by each maneuver. The corium consists mainly of the already-described connective tissues, which are regarded as the water stores of the body (3). Therefore, it can be concluded that the shift from the vascular to the extravascular compartment essentially takes place in the corium. Surprisingly, the sum of corium thickness and subcutis thicknesses did not show that pattern. We assume that the investigator tended to compress the skin by the ~4-cm straight but narrow surface with a convex sectional area of the B-mode probe, with the intention of image improvement by good skin contact. These circumstances would also explain the respective decrease of subcutis thickness, which mainly consists of fatty tissues that are more easily compressed than connective tissues. Furthermore, they account for the positive bias of 0.48 mm between tissue thickness and the sum of chorium and subcutis thicknesses. In contrast, the A-mode device is equipped with a planar probe (circular surface = 314 mm²), which is held by its own weight, diminishing the risk of skin compression.

It must be noted that there are caveats associated with tissue thickness monitoring using the miniature ultrasound A-mode device. Tilting of the transducer must be carefully avoided, but it is unlikely because of the planar shape of the contact surface of the probe. The underlying bone of the forehead presented an almost plane surface and hence good reproducible backwall echoes in our study. Furthermore, no blood vessels other than the capillaries could be detected in the area of investigation. We had to ensure that all measurements were carried out by a single investigator to guarantee uniform study conditions. Nevertheless, it has to be noted that ultrasonic measurements, whether A or B mode, inherit the danger of contestability due to investigator-dependent variability.

In conclusion, fluid shift from the intravascular to the extravascular compartment was easily detectible by evaluating superficial tissue thickness with a miniature A-mode ultrasound device. Similar results were derived by measuring corium thickness by B-mode ultrasound. A disadvantage of the B-mode device is the narrow and rounded probe, which seems to cause skin compression.

The corium contains one-third of total interstitial fluid volume and is mainly responsible for changes in skin thickness by increased net capillary filtration.
Therefore, focusing interest on peripheral tissue thickness appears reasonable and comprehensible. The use of ultrasound devices may allow a better understanding of the kinetics of peripheral tissue volume and fluid distribution. Finally, they provide an alternative to more invasive methods of fluid therapy monitoring.

REFERENCES