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TISSUE TONOMETRY: A USEFUL TOOL FOR ASSESSING FILARIAL LYMPHEDEMA

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ABSTRACT

A tissue tonometer was used to assess peripheral lymphedema in patients with filariasis in a Bancroftian endemic community. Matched populations of 34 patients with Grade II and 29 patients with Grade III unilateral lower limb edema and 26 healthy subjects were assessed for leg tissue compressibility and circumference. Tonometry was performed at three fixed points on the leg using three weight levels (70, 140, and 210gms). The mean value of compressibility for each weight level and points measured in the edematous leg were significantly less compared with the contralateral non-edematous leg in the filarial patients and the legs of healthy subjects. Patients with Grade III lymphedema were more resistant to compression than Grade II patients throughout the leg but especially at the foot. The least mean square analyses of circumference and compressibility differential values of edematous compared with non-edematous legs revealed a positive correlation at the foot in Grade II and the proximal and distal parts of Grade III lymphedema; moreover, the slopes were significantly different from zero. These findings support progressive tissue changes of edema and fibrosis first in the foot and later in the more proximal portions of the leg which correspond to progressive volume expansion with protein-rich fluid. Tissue tonometry appears to be a sensitive measure for assessing progression of both edema and fibroplasia in patients with peripheral lymphedema associated with filariasis, and, therefore, may be a useful tool to measure the efficacy of drugs commonly used to treat this condition.

Lymphedema, the commonest form of clinical presentation in human filariasis results from the failure of the lymph transport system due either to functional or obstructive lesions of regional lymph vessels. Repeated acute episodes of regional adenolymphangitis followed by peripheral lymphatic sclerosis and eventual occlusion is considered the hallmark in the pathogenesis of filarial lymphedema (1). However, because of ongoing physiologic adjustments such as formation of new lymphatic collateral pathways as demonstrated by lymphography (2,3), the body seems to overcome the initial lymphatic blockage so that edema usually subsides after the acute or early stage. Nonetheless, in some patients the stagnant protein-rich tissue fluid eventually leads to extensive tissue proliferation and a grotesque appearance to the affected part. The underlying pathogenesis in filarial lymphedema is probably not radically different from that of other secondary or acquired lymphedema syndromes.

Some investigators have examined filarial lymphedema by measuring dimension and volume changes using circumference measurement and fluid displacement of an affected limb compared with the non-edematous extremity (4,5). Whereas these techniques reflect changes in limb volume they do not address the underlying pathophysiology. Moreover, there is no acceptable standardized method for monitoring filarial lymphedema.

Tissue tonometry has been successfully used to assess other secondary lymphedemas by measuring tissue compressibility. Indirectly, this technique reflects the degree of "browniness" or of tissue remodeling and fibroplasia (6,7). The present study aims to evaluate the usefulness and sensitivity of tissue tonometry in patients with filarial lymphedema and compare the findings with serial limb circumference measurements.

MATERIALS AND METHODS

Patient Selection

After a detailed clinical and parasitological survey, patients from a Bancroftian endemic area of the Puri district of Orissa with chronic filariasis and unilateral leg edema were selected. The extent of the edema was classified into three grades according to criteria of the International Society of Lymphology for secondary lymphedema (8):

Grade I: Mostly pitting lymphedema, mild fibrosis, edema remits on limb elevation.

Grade II: Mostly non-pitting lymphedema, considerable fibrosis, non-remission on limb elevation.

Grade III: A profound increase in limb volume from lymphedema, marked dermatosclerosis, with or without skin papillomata.

63 patients with intractable lower limb edema were examined including 34 with Grade II and 29 with Grade III lymphedema. The contralateral non-edematous leg served as a control. Twenty-six healthy subjects from the same village were similarly studied, matched for age and gender with a similar occupational background (laborers).

Tissue Tonometry

A second generation tissue tonometer obtained from COMPAC, Switzerland designed by Clodius and Antoniazzi was used to evaluate tissue compressibility of the legs. This tonometer after calibration numerically determined in arbitrary units the hardness or softness of normal or altered tissue. In the center of the foot plate, a plunger of one centimeter diameter was added with a complementary weight to exert 70 gram weight on the skin. Onto this column two successive weights of 70 gram were loaded to measure the corresponding deflection by the tonometer. The distance of plunger depression of the central column into the tissue at three different weights (70, 140, and 210 grams) was recorded on a graduated scale. One millimeter tissue depression corresponded to 100 units on the scale. Thus, three different measurements were obtained for three separate weight ranges at a fixed point.

Clinical Measurements

Tissue compressibility

Tissue compressibility was measured in the leg at three fixed points, (a) on the dorsum of the foot between the first and second interphalangeal joints, (b) distal part of the leg, 15cm above the ground, (c) proximal part of the leg at 30cm above the ground. The latter two measurements were done on the calf with the patient prone and the soleus-gastrocnemius muscles relaxed. The values were recorded for each successive weight while keeping the tonometer vertically free. The mean value after three separate measurements at each weight level was used for statistical analysis.

Circumference

Limb circumference was measured using a standard centimeter tape at consistent leg sites. Measurements were taken without the examiner knowing the lymphedema grade classification.

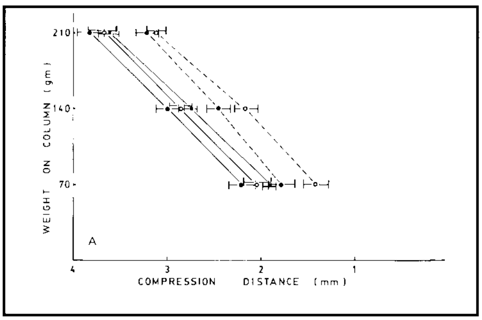
Statistical Analysis

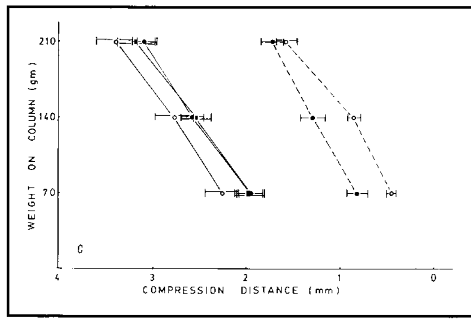
For comparison of mean tonometric and circumference values, a student t-test was performed. A least square analysis was used for the different values of the non-edematous and edematous limb.

RESULTS

Tissue Compressibility

The tissues of longstanding lymphedema were consistently more resistant to compression than that of the non-edematous apparently healthy counterpart at each weight level ($p<0.05$ to $p<0.001$) *(Fig. 1)*. Decreased tissue





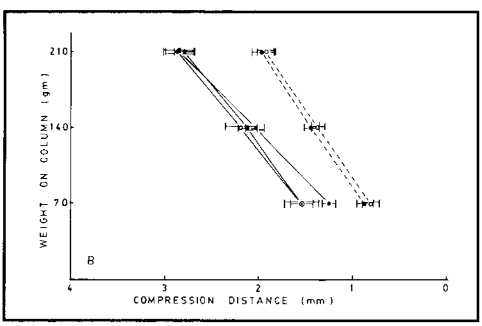
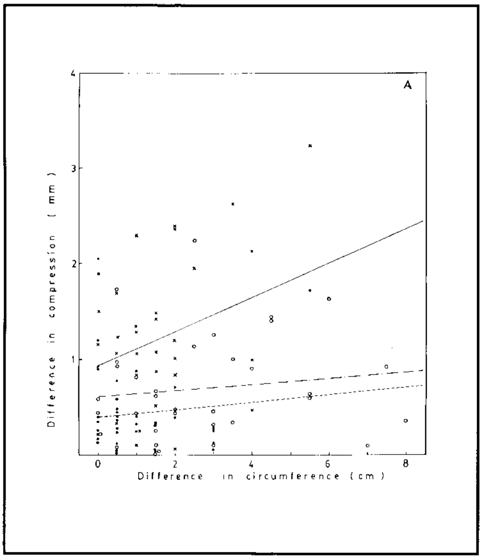


Fig. 1. Mean±SEM distance of compression at three weight levels measured in Grade II, non-edematous leg (•——•) and edematous leg (•------•), Grade III non-edematous leg (o——o) and edematous leg (o ——-o), and healthy subjects with non-edematous legs (■ ——-■). A: proximal leg; B: distal leg; C: foot.

TABLE 1
Least Mean Square Analyses of Circumference Difference Versus Mean Compression Difference (see Fig. 2)

Lymphedema Grade	Leg Part	Intercept	Slope	Correlation Coefficient
II	Proximal	0.390	0.036	0.105
	Distal	0.626	0.029	0.116
	Foot	0.949	0.190	0.316*
III	Proximal	0.409	0.062	0.256*
	Distal	0.363	0.044	0.228*
	Foot	1.691	0.039	0.091

*$p<0.05$ (one-tailed test)



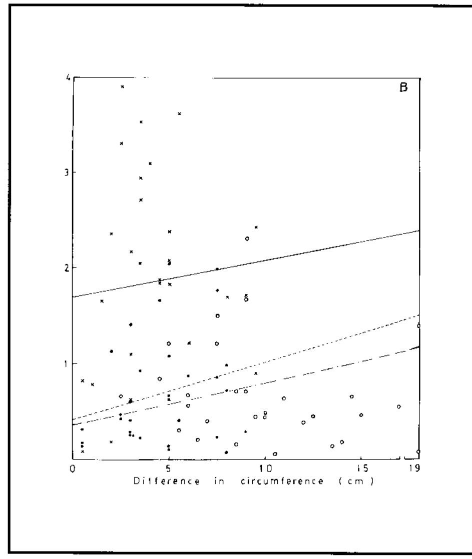


Fig. 2. Least mean square analysis of circumference difference vs. compressibility difference of edematous and contralateral non-edematous leg in patients with Grade II (left) and Grade III (right) filarial lymphedema. Proximal leg (•), distal leg (o), and foot (X).

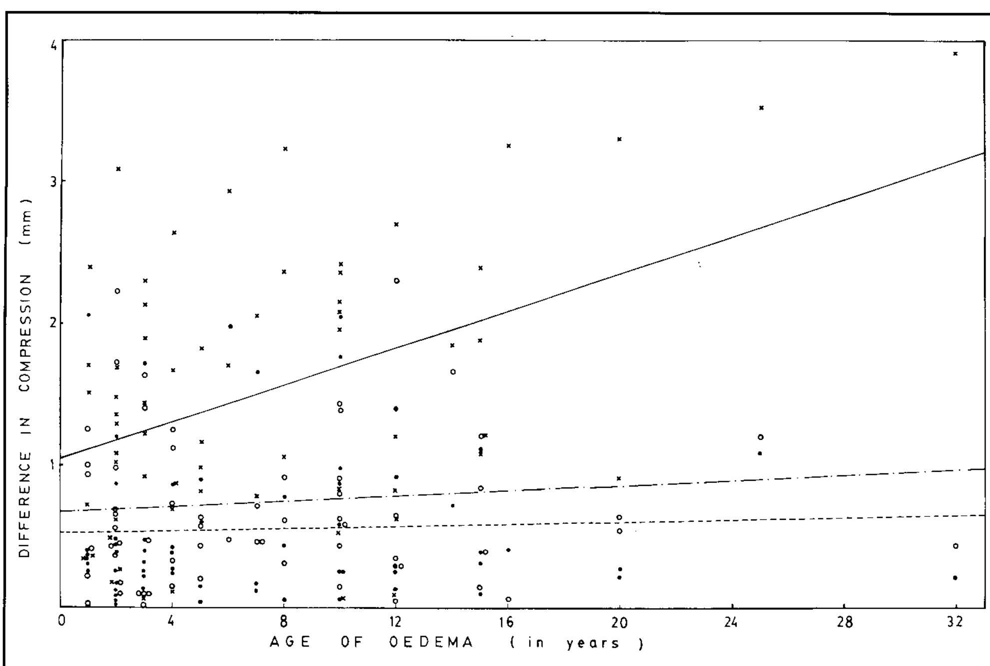


Fig. 3. Least mean square analysis of duration of lymphedema vs. compressibility difference of edematous versus non-edematous contralateral leg. Proximal leg (•), distal leg (o), and foot (X).

compressibility was found for both Grade II and III lymphedematous legs. The difference of compression of the edematous leg compared with the non-edematous contralateral leg was most pronounced at the foot *Fig. 1***C**). The leg tissue compressibility of healthy subjects was similar to that of the non-edematous contralateral leg of patients with filarial lymphedema at all points and weight levels tested *(Fig. 1***A-C***)*.

Tissue Compressibility vs. Circumference Difference

The least square analysis denoting the change in compressibility for each measurement of circumference are depicted for Grade II and Grade III lymphedema patients in *Fig. 2*. The slope, intercept, and correlation coefficients of the comparisons are summarized in *Table 1*. The slopes for the proximal and distal part of the leg in patients with Grade III lymphedema (but not Grade II) were significantly different form zero. At each point of the edematous leg, the tissue became resistant by 0.062mm and 0.044mm for each centimeter increase in circumference. On the other hand, in the foot, the slope was significantly different from zero in the Grade II lymphedematous leg (but not Grade III). For each centimeter increase in diameter, the tissue became more resistant to compression by 0.2mm. The difference in circumference was also significantly correlated with compressibility at the foot in Grade II lymphedema (one-tailed test). The difference was also weakly correlated at the proximal and distal part of the leg in Grade III lymphedema.

Duration of Edema vs. Tissue Compressibility

The difference of tissue compressibility at each leg site was compared with the duration of lymphedema as obtained by patient history *(Fig. 3)*. The least mean square analysis provided the following: For the proximal and distal leg and foot, the intercepts were 0.52, 0.65, and 1.05, respectively, whereas the slopes were 0.004, 0.01, and 0.065, and the correlation coefficients were 0.05, 0.12, and 0.434, respectively. These data suggest that with time the foot is more resistant to compression than either the proximal or distal leg. This value rose by ~0.07mm yearly as the lymphedema progressed.

DISCUSSION

The pathogenesis and progression of filarial lymphedema is not fully understood. However, the pattern of peripheral edema development following repeated regional lymphangitis suggests progressive inflammatory damage of the transporting lymph vessels. It still remains to be elucidated whether lymphatic injury is mediated by the parasite directly or through host immunoreactivity or indeed involves other non-recognized biologic phenomena altogether. Although lymphedema involving the extremities is common, only a small portion of these patients slowly or rapidly progress to elephantiasis. Hyperplasia and fibrosis of the subcutaneous tissue and thickening of the skin constitute the major pathological change in elephantiasis (9). Moreover, functional lymphatic incompetence accompanied by progressive lymphatic damage leads to failure of central lymph transport with the accumulation and stagnation of protein-rich edema fluid in the tissue spaces. In large part, development of lymphedema in patients with filariasis simulates other acquired or secondary peripheral lymphedemas. For example, in patients after radical mastectomy, the high protein arm lymphedema favors tissue fibroplasia, fibrinogenesis and gradual obliteration of peripheral lymph channels and unremitting lymph stasis (7). By this process, the initial soft stage of lymphedema is gradually transformed into a hard, brawny late stage lymphedema. Perhaps stagnant protein-rich edema fluid that persists in the tissue compartments for a long period stimulates continuous tissue fibrosclerosis (7). Occasionally, local tissue overgrowth is excessive and the nodular deformities that develop in the lymphedematous extremity take on the appearance of an elephantine pedestal.

The proliferation of lymphedematous tissue is likely determined by the number of remaining functioning lymphatics and the interstitial pressure which, in turn, depends on the elasticity of the skin (7). The more elastic the skin, the more the limb can expand. In longstanding filariasis with extensive fibrosclerosis, the skin gradually loses its elasticity thus inhibiting further volume expansion. At this stage, progressive pathological changes in the tissues occur without corresponding increase in volume. Instead, areas of fibrotic contraction may paradoxically decrease limb circumference. As edema fluid is gradually replaced by proliferating fibroplasia with loss of skin elasticity, the changes can be documented by serial tissue tonometry. Circumference or volume displacement measurements which test solely for limb dimension may at this stage give misleading information about the extent of pathologic abnormalities in the presence of diffuse fibrosis. Volumetric techniques (4,5) also have other inherent disadvantages. Thus, limb volume measurement by water displacement requires use of an unwieldy measuring device which must be carefully placed on a horizontal plane to avoid viewer "parallax" along with liquid spillage during limb insertion into the receptacle. These drawbacks make use of this measuring technique inconvenient in remote locales. Circumference measurements taken at various limb sites also may yield misleading values when an edematous limb with multiple nodular and pouch-like deformities is encountered. Structural and functional alteration of peripheral lymphatics can more clearly be delineated by lymphangio-scintigraphy (10), but it too has logistical limitations in assessing lymphedema of a large endemic population. Because tonometry measures tissue consistency in terms of compressibility, it provides reliable information on the state of persistent lymphedema as previously demonstrated in patients with radical mastectomy for treatment of breast cancer (6,7).

Greater incompressibility was seen in the edematous legs of patients with filariasis compared with the non-edematous contralateral leg or healthy control leg *(Fig. 1)*. This finding was especially true in the foot region in both patients with Grade II and III lymphedema *(Fig. 1C)*. Because the foot is the most dependent structure, it is most prone to edema, injury, infection and therefore tissue fibrosis particularly in patients who reside in rural communities. The differential compressibility of lymphedematous legs compared with non-edematous legs and correlation with circumference increase at the foot in patients with Grade II lymphedema and more proximal portions of the leg in patients with Grade III lymphedema suggest the earliest tissue changes occur initially in the foot and later more proximally as interstitial volume increases (Grade III). Lack of correlation of volume expansion with compressibility above the foot in Grade II lymphedema is probably due to edema accumulation without much fibrosis and subsequent loss of compressibility. Foot lymphedema in Grade III patients probably signifies that volume expansion is limited beyond that where the tissues show resistance to compression. Although the data collected on duration of leg edema is historical and therefore more subjective, the findings nonetheless suggest that longer duration and presumably greater tissue fibrosis is correlated with progressive skin incompressibility at the foot.

Because no notable difference was detected in the tonometric values of contralateral, non-edematous legs of patients with filariasis and legs of healthy subjects, it seems appropriate to compare the mean compressibility in patients with bilateral lymphedema with healthy but otherwise matched controls from a standardized population.

Tonometry is a promising indicator of pathologic alterations occurring in the lymphedematous limbs of patients with filariasis including the nature and extent of the disease process (i.e., either volume expansion, fibrosis, or both). A tissue tonometer is easy to handle and convenient to operate, and therefore may be a useful tool to complement volumetric techniques and to assess the efficacy of putative chemotherapeutic drugs (e.g., diethyl-carabamizene, ivermectin, benzopyrones) commonly used to treat this disorder.

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