Novel insight into the pathophysiology of breast-cancer-related lymphoedema

In this issue of Clinical Science, Stanton et al. [1] describe experiments that provide new insights into the pathophysiology of breast-cancer-related-lymphoedema (BRCL), a condition affecting a quarter of patients successfully treated for breast cancer by mastectomy, associated lymph node removal, and/or subsequent radiotherapy. BRCL has long been considered a result of reduced lymph flow through damaged lymph nodes. Evidence in support of this comes from lymphangiography experiments, where radioactive tracers injected into peripheral lymphatics take longer to reach the axilla in the swollen arm than in the normal arm, and from lymphoscintigraphy studies, where the removal rate of radioactive tracers from lymphoedematous tissue is significantly reduced compared to the normal, contralateral arm.

Levick and Mortimer [2] have pointed out previously that lymphangiography studies only measure the speed at which lymph is moved and not the rate of flow, since that would depend on the volume of the lymph system. Lymphoscintigraphy measurements are affected by the volume of fluid in the local tissue (distribution volume) that the lymphatics are draining. Although these studies cannot measure lymph flows (since the distribution volume is not known), they can be used to measure how well lymphatics drain a unit volume of fluid. In this issue of Clinical Science, Stanton et al. [1] have shown that, although the clearance rate of radioactive substances from the swollen tissue of the affected arm is significantly lower than that of the contralateral arm, this is not the case for the non-swollen areas of the affected arm. In fact, in the non-swollen areas of the affected limb, the drainage of fluid is faster than in the normal arm. This has two important implications for our understanding of this condition. First, it lays the blame for the swelling firmly on lymphatics in the swollen areas of the arm. In the non-swollen tissue, the lymphatics still have to drain fluid through the damaged axilla, yet clearance is actually increased. One explanation for this finding is that the lymphatics in the swollen area are unable to cope with the increased resistance to flow and have become failing vessels, analogous to the heart in congestive cardiac failure. The result of this inefficiency of the lymphatics is that a higher interstitial pressure is needed to drive the fluid flow along the lymphatic vessels. It is the swelling that provides this higher interstitial pressure in lymphoedematous regions of the arm.

The second implication of these studies is that if there is higher clearance from the non-swollen parts of the affected arms than the normal arms, then, since these tissues have the same distribution volume, the lymph flow in the non-swollen part of the affected arm must be increased relative to the contralateral normal tissue. As these tissues are neither swelling nor shrinking, then the rate of fluid movement into the tissue must equal the rate of fluid removal from the tissue. It is not clear whether this increased rate of movement of fluid into the tissue represents increased filtration across the vascular wall or flow from the swollen areas of the limb through the subcutaneous spaces. The removal rate described by Stanton et al. [1] was from the finger web, some considerable distance from the nearest swollen region, and therefore increased fluid filtration is the most likely explanation for this increased clearance. Fluid formation therefore appears to be increased in the non-swollen parts of the affected arm. This is not the first time that evidence has been presented in Clinical Science for increased filtration rate in lymphoedema. In 1993, Bates et al. [3] compared the protein concentrations of lymphoedematous arms to normal arms and showed that the larger the arm, the lower the protein concentration. Again, since the arms were in a steady state, this was interpreted as evidence for increased rate of fluid formation, without increased protein extravasation (since interstitial protein concentrations are inversely proportional to filtration rate).

Furthermore, Stanton et al. [1] have extended the normal methods for measuring clearance rates of fluid from tissue, as they have also measured the rates of spread of the radioactive substances from the injection site. It may be possible to use these rates of spread to estimate the relative changes in lymph flow in the affected versus unaffected arms. If the permeability of the tissue to diffusion and convection of radioactive substances is the same in the swollen and normal arms, and the radioactive depot is of sufficient magnitude, then the relative local tracer flux in the affected compared with the normal arm will be proportional to the relative distribution volumes. Since the clearance rates are also known, then the lymph flows can be estimated. When these calculations are applied to the data of Stanton et al. [1], estimates of lymph flow are actually 20% higher in the swollen tissue than in the contralateral normal arm. In other words, the lymph flow is increased even in the swollen part of the lymphoedematous arm. Therefore the reason why the oedematous tissue is swollen is not because the lymph...
flow is less, but that a higher pressure is necessary to maintain the same or higher lymph flow, i.e. the response of the lymphatics to increased fluid in the tissue is not as great in the swollen regions as it is in the normal regions.

This finding raises two particularly interesting points for lymphoedema treatment. Until we know how the lymphatics respond to interstitial forces to increase the flow rate, we will not be able to restore the efficiency of the lymphatics in BRCL. It will therefore be necessary to measure quantitatively the relationship between interstitial pressure and lymph vessel activity. In addition, the filtration rate in the superficial tissues of the arms of lymphoedema patients appears to be higher than in the normal arm, implying that either capillary pressure is increased in these tissues or the permeability of the capillary wall to fluid is increased in these patients. The underlying reason for this is still unknown. It is therefore likely that the findings that Stanton et al. [1] may provide the basis for a new understanding of the pathophysiological mechanisms that underlie this common, disfiguring and debilitating condition.

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(ON BEHALF OF THE EDITORIAL BOARD)

REFERENCES