Transepidermal Water Loss

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The use of noninvasive measurement methods for the examination of different physiological functions of the skin or for the characterization of pharmacological or pathological reactions is recent. Following the development of suitable techniques, instruments are now available for the evaluation of such different cutaneous parameters as color, elasticity, dermal blood flow, hydration of the horny layer, sebum excretion, and, of course, transepidermal water loss (TEWL). This equipment may replace the usual visual evaluation of skin state and are able to catch changes that otherwise would be not detected by the human eye.

Numerous advantages arise from using these techniques: independence toward investigator's subjectivity, numerical results and not ordered nominal data, better standardization of the experiments, better possibilities of interlaboratory comparisons, no requirement of highly specialized personnel, etc. For all these reasons, these new techniques are of growing interest for dermatological laboratories. Moreover, the increasing automation of data acquisition allows for the simultaneous evaluation of several parameters if necessary.

1 Transepidermal Water Loss

1.1 Basic Physiological Principles

Water has two possibilities in crossing the skin from the viable tissues toward the outer environment: active transport by sweating and passive diffusion through the horny layer. Sweating (*perspiratio sensibilis*) is one possibility for the body to control its temperature. It may also express psychic stress. Sweating may peak at maximal values of 2–4 l/h. On the contrary, transepidermal water loss (TEWL, *perspiratio insensibilis*) is not visible to the naked eye. Given no air turbulence, the skin is covered by a transition layer where moisture is transferred from the surface of the skin to the surrounding atmosphere, building up a protective sheet toward environment. The quantity of water crossing the stratum corneum on this way is estimated at 300–400 ml per day under normal conditions, that means 1/10th to 1/20th of sweating. Given this difference, it is mandatory to eliminate sweating during TEWL measurements. (Note: Water loss due to expired water vapor is also included in the term *perspiratio insensibilis*. But for the sake of clarity, only water loss through the horny layer will be considered here.)

1.2 Theoretical Principles

The diffusion barrier is situated entirely within the horny layer (Wilson and Maibach 1989; Lévêque 1989). The TEWL is a passive phenomenon due to the water vapor pressure gradient on both sides of the layer. Water concentration in the epidermis, which is well hydrated in contact with the dermis, is estimated to be 48–49 mol. This value is also found at the deeper side of the horny layer. On the other side, water concentration at skin surface, which is in contact with drier surroundings, is lower and was shown to be around 12 mol (ambient conditions: relative humidity 40 %, temperature 31 °C). The pressure gradient thus amounts to 37 mol (Wilson and Maibach 1989). Thus, if the relative humidity of the surrounding air is 100 %, the TEWL will decrease almost to zero, and inversely, if the relative humidity is 0 %, TEWL will be maximal (Fig. 1).

Passive diffusion of water through the horny layer is described by the 1st Fich's law (Schaefer and Redelmeier 1996). At equilibrium, the flux of water (J, mol cm^{-1} s^{-1}) travelling upon a given distance (δ, cm) is proportional to the concentration gradient (ΔC) and to the diffusion coefficient

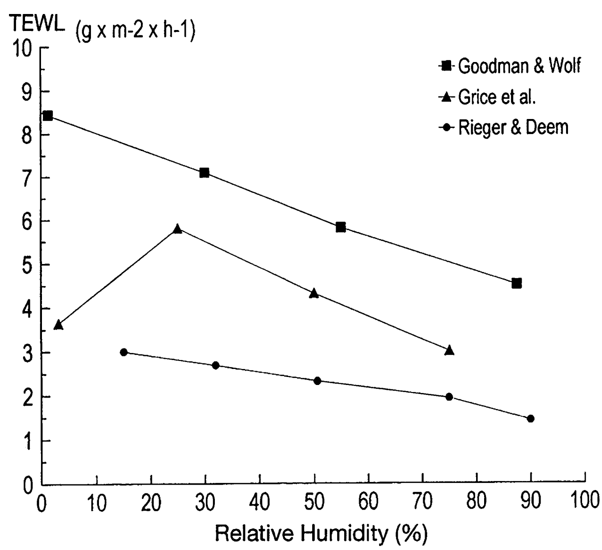

Fig. 1 Effect of relative humidity on TEWL: results of three studies

(D, cm^2/s). However, the horny layer is not an inert membrane, but shows some affinity to water and Fick's law needs to be modified by the introduction of a partition coefficient K_m (Wilson and Maibach 1989; Potts and Francoeur 1991):

$$K_m = \frac{(\text{Water concentration in the lower horny layer})}{(\text{Water concentration in the intercellular space of living epidermis})}$$

Fick's law thus writes $J = -K_m \times D\,(\Delta C/\Delta\delta)$

K_m amounts to 0.06 (Potts and Francoeur 1991). The negative symbol "−" shows that the flux is directed toward lower concentrations.

2 Methods and Measurement Devices

2.1 Introduction

Different measurement methods were described by Wilson and Maibach (1989). Briefly they list:

- Urine osmolarity
- Body weight
- Closed cylinder method: weight of an hygroscopic substance
- Ventilated chamber
- Electrohygrometer
- Thermal conductivity cell
- Dew-point hygrometer
- Electrolytic water vapor analyzer
- Open cylinder

This list is not exhaustive. The results obtained using these different methods are hardly comparable because of the difficulty in measuring TEWL under standardized conditions and the importance of several variation factors (see Sect. 3). A recently published review (Pinnagoda 1994a) shows that the measured values may depend, within certain limits, on the method employed. Wilson and Maibach (1989) described these different techniques with their advantages and drawbacks, but some of these are obsolete and/or not commercially available. For these reasons, only the last one, the most commonly used, will be described. Several instruments are commercialized using the open cylinder method for measurement, and recent reviews describe this method in detail (Pinnagoda 1994a; Pinnagoda and Tupker 1995).

2.2 The Open Cylinder Method

A probe is applied on the skin surface, built as a cylindrical chamber open to the surrounding air. A 0.8–1 cm^2 skin area (value depends on the instrument) is delimited by the probe and constitutes the bottom of the chamber. Two sensors (semiconductors) measuring relative humidity are situated at two different levels vertically in the chamber. Each is coupled to a thermistor (Fig. 2). The distance from the sensors to the skin surface is calculated for an optimal evaluation of the water vapor pressure gradient arising within the chamber between the skin and the surrounding air.

Water pressure at each level is calculated from the following equation:

$$P = RH \times p_{sat}$$

p_{sat} is pressure at water saturation. Relative humidity (RH: %) is measured by the semiconductors; p_{sat} is calculated by the instrument, given the air temperature at each sensor level. The vapor pressure difference between the two measurement levels determines the slope of the pressure gradient. The TEWL is directly expressed in $g\ m^{-2}\ h^{-1}$.

2.3 Instruments

Several instruments using the open cylinder method are available: the Evaporimeter, the

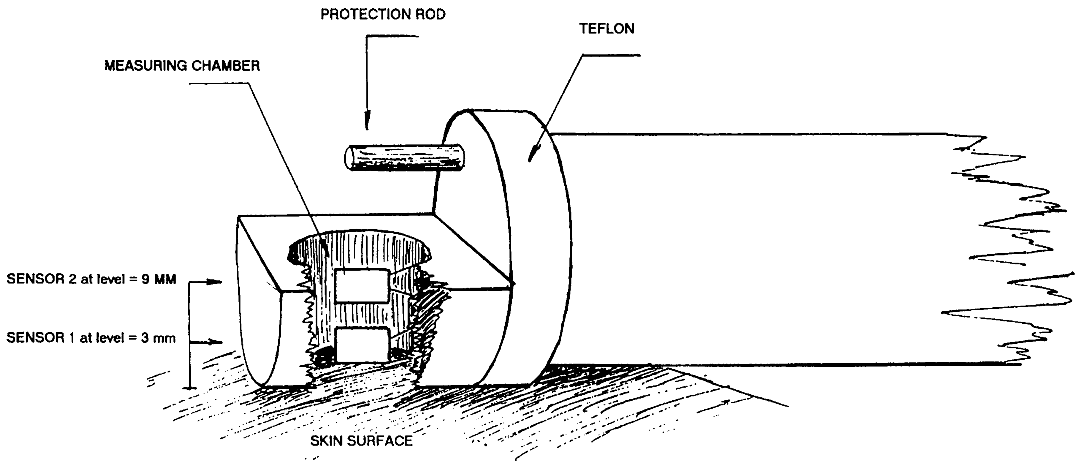

Fig. 2 Schema of the TEWL measuring head

Tewameter, and more recently the DermaLab (for manufacturer's location, see Evaporimètre®; Tewamètre®; DermaLab®). An evaluation of both the Evaporimeter and the Tewameter and a comparison of the results obtained with these machines were published by Barel and Clarys in 1995 (Barel and Clarys 1995a, b). A similar comparative evaluation of the DermaLab and of the Evaporimeter was recently published by Grove et al. (1999). This last publication also lists previous reports dealing with comparative performance studies of the Evaporimeter. The geometry of the measuring probe and possibly the manufacturer's calibration method vary slightly between the different instruments, as well as the electronic treatment of measured data. Although the values obtained with one instrument are highly correlated to the values obtained with the other, some differences may remain between the values and between their variations after a given challenge (Barel and Clarys 1995b; Grove et al. 1999).

A portable device has recently been put on the market: Model H4300 (Nikkiso YSI Company Ltd, Tokyo, Japan). Its principle is based on the progressive increase in relative humidity inside a closed chamber, due to continuous water evaporation from the skin surface on which the chamber is placed. A linear correlation was found with DermaLab ($R^2 = 0.917$), but the obtained values were much lower (Tagami et al. 2002).

3 Sources of Error, Standardization, and Practical Recommendations

3.1 Introduction

Because of the dependency of the TEWL on the water vapor pressure gradient on the skin surface, every intrinsic or extrinsic factor influencing either the thickness of the transition layer from skin surface to surrounding air or the slope of the gradient within the transition layer will modify the TEWL. Moreover, given the sensitivity of the measuring probes, any change in the environmental microclimate will be detected and will consequently modify the indicated values unless the measuring conditions have been rigorously standardized. Precise recommendations concerning this particular point have been published (Pinnagoda et al. 1990; Rogiers 1995; Pinnagoda 1994b).

3.2 Sources of Error and Variation Factors

Variation factors may be classified as follows:

- Instrumental factors
- Environmental factors
- Individual factors

These factors have already been extensively reviewed (Pinnagoda and Tupker 1995; Barel and Clarys 1995b; Grove et al. 1999; Pinnagoda et al. 1990; Rogiers 1995; Pinnagoda 1994b) and listed (Pinnagoda et al. 1990), and their relative influence has also been evaluated. For these reasons, the interested reader will consult the original publications for more details.

- Instrumental factors
  - Preheating of the instrument: at least 15 min for electronic circuit stabilization. It is not recommended to switch off the instrument between the measurements.
  - Instrument zeroing: After preheating, under measuring conditions (see Sect. 3.4).
  - Measurement technique (see Sect. 3.4 and Pinnagoda et al. (1990); Rogiers (1995)).
  - Variation of zero during the measurements: to be regularly controlled.
  - Humidity and temperature variations in the open chamber: the probe must not be left in place on the skin; avoid contact with sweat.
  - During measurements the probe should remain horizontal.
  - Use of a protecting grid to avoid contact with a test product applied on the skin.
  - Pressure of the probe onto the skin.
  - Regular calibration of the probe following the manufacturer's instructions and as requested by GLPs.
  - Inter-instrumental variations (see Grove et al. (1999); Pinnagoda et al. (1990)).
  - Precision of the measurements (see Sect. 3.3).
- Environmental factors
  - Air convection and turbulences during the measurements
  - Environmental temperature
  - Environmental humidity
- Individual factors
  - Sweating
  - Skin temperature
  - Anatomical location of the measurement
- Conclusions

The relative importance of these factors is not the same. If a minimal standardization is assured, instrumental factors are less important. The greatest variations are then due to the environmental and individual factors. Figures 3, 4 (Barel and Clarys 1995b), and 5 (Van Kemenade 1998) illustrate, for example, the respective influences of the environmental temperature or relative humidity on measured values. Figure 5, showing recent data, is of particular interest: a sudden variation of the relative humidity from 53 % to 89 % provokes a fall of the TEWL, which thereafter slowly returns but stabilizes at a level lower than starting values. This last phenomenon is due to a change of the hydration of the horny layer, which also depends on the environmental

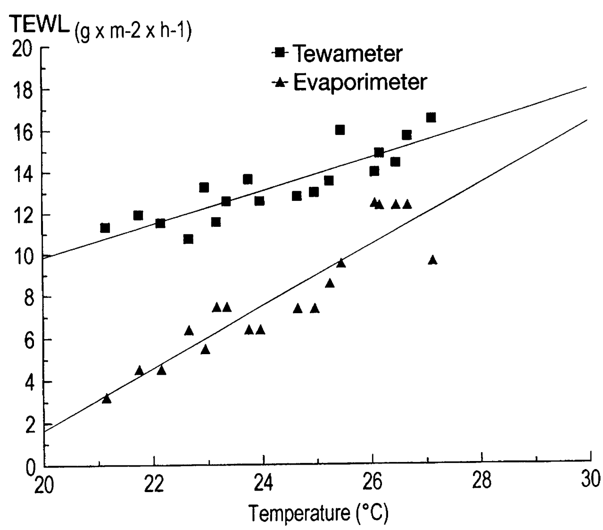

Fig. 3 Forearm TEWL versus ambient temperature, as measured with Evaporimeter and Tewameter

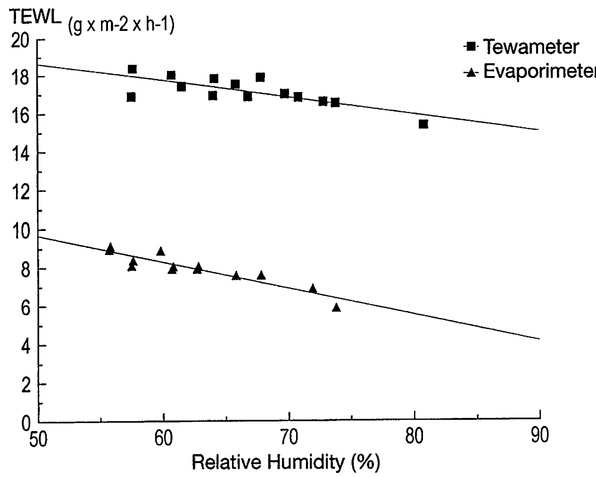

Fig. 4 Forearm TEWL versus ambient relative humidity, as measured with Evaporimeter and Tewameter

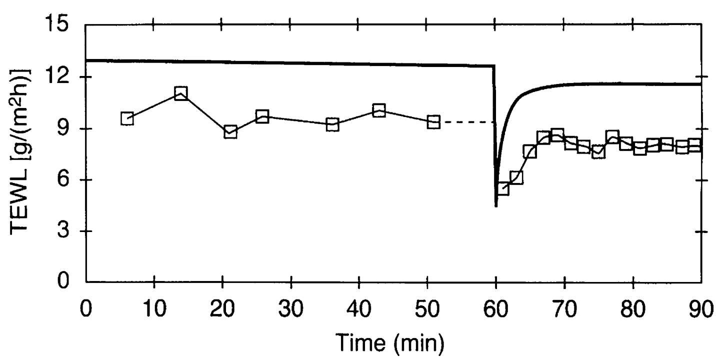

Fig. 5 TEWL versus sudden change in ambient relative humidity: within 1 h TEWL raised from 53% to 83%. Line with open squares measured TEWL, black unbroken line modelled TEWL

relative humidity. As to the individual factors, variations between to different anatomical are shown in Table 1 (Clarys et al. 1997).

3.3 Precision and Reproducibility of the Measurements

- Precision

  The following data are given by the manufacturers:

  – Evaporimeter: Precision ± 15 % (EP 1), ± 5 % (EP2)
  – Tewameter: Precision ± 15 % (±1.0 g m^{-2} h^{-1} if RH < 30 %), ± 10 % (±0.5 g m^{-2} h^{-1} if RH > 30 %)

The precision of the measurements is difficult to check, because the exact value of the TEWL must be measured using a gravimetric method (Wilson and Maibach 1989; Barel and Clarys 1995b). If such measurements are made, it appears that a correction is necessary to obtain absolute values (Petro and Komor 1987), particularly if these values are high and exceed 50 g m^{-2} h^{-1} (Pinnagoda and Tupker 1995; Petro and Komor 1987). This correction is given by the following equation:

$$TEWL_{corr} = Bx^{k}$$

where B is the measured TEWL value (g m^{-2} h^{-1}), x a constant (x = 0.025 cm),

Table 1 Table 1 Mean TEWL for various sites of the body measured with a Tewameter. Mean ±S.D for 16 volunteers

Body site	TEWL (g/m^2h)
Forehead	20.1±4.8
Chest	10.7±1.3
Abdomen	9.9±1.8
Forearm (inner surface)	10.4±3.1
Calf	9.6±1.8

and k the slope of the line: [logTEWL = f (distance between the lower sensor and the skin surface)]. k has been determined for measurements on the volar forearm: k = −0.049 (Petro and Komor 1987).

- Reproducibility

  The reproducibility of the measurements is good if the measuring conditions have been standardized. Barel and Clarys (1995a, b) found variation coefficients between 3 and 8 %. Pinnagoda et al. published slightly higher values between 8 % and 15 % (Pinnagoda et al. 1989). Grove et al. (1999) published coefficient of variations of 4–47 % depending on the type of equipment used and on the level of the measured values (higher variations encountered if low values are measured).

3.4 Practical Recommendations

The control of environmental factors is only achieved by conducting the measurements in an air-conditioned room, featuring temperature, and relative humidity control. Turbulences and air convection in the near surroundings of the measuring probe are best eliminated by conducting the measurements inside a protecting box, e.g., an incubator with holes for the placement of the forearms (Pinnagoda et al. 1990). An open top should avoid buildup of temperature and water vapor inside the box. The measuring plane should remain horizontal, thus allowing the gradient to be built correctly in the measuring chamber. The pressure of the probe on the skin should remain low.

Control of individual factors is achieved by a strict selection of the study subjects, by allowing enough time for their relaxation before entering the experimental phase of the study ensuring their perfect adaptation to the controlled environmental conditions. For example, it is important to distinguish between atopic and non-atopic subjects, because the TEWL of atopic subjects is elevated in comparison to non-atopic ones, even if the skin of the atopics looks normal. Adaptation to the environmental conditions requires at least 20 min before measurements start. An experimental protocol should be available (Salter 1996), which excludes, for example, subjects having ingested spiced food that may provoke sweating. Stress also may provoke sweating; therefore, individuals should be thoroughly instructed and allowed to relax completely before starting with the study. These conditions ensure better reproducibility and precision of the measurements.

TEWL is tightly correlated to the barrier function of the horny layer. On the other hand, the barrier function also depends on the water content of the horny layer. The relationship between TEWL and the stratum corneum hydration must be considered in particular situations such as in newborn babies or old people or in measurements on a diseased skin (Berardesca and Maibach 1990).

Last but not least, some components of dermatological products may influence the measured values. Morrison (1992) showed that propylene glycol in a formulation could lead to an overestimation of the TEWL due to an interaction of this compound with the measuring probe. Dermatological or cosmetic products contain water that evaporates following application, and this evaporation adds to the underlying TEWL for a certain time. In this case, the measured value is known as skin surface water loss (SSWL). SSWL is also encountered during such particular experiments as the plastic occlusion stress test (POST) featuring a prolonged skin occlusion leading to water accumulation in the horny layer (Berardesca and Maibach 1990; Berardesca and Elsner 1994).

4 Practical Examples

Lastly, some practical examples of the use of TEWL are described in experimental and, more briefly, in clinical dermatology.

4.1 Experimental Dermatology

- Skin barrier function

  The results obtained by the group of A. Rougier (1994) or of M. Ponec (Oestmann et al. 1993) show a tight relationship between TEWL and the penetration of some chemicals through the skin, such as benzoic acid, acetylsalicylic acid, caffeine, or hexyl nicotinate. This relationship may still be valid in some pathological situations (Lavrijsen et al. 1993).
- Skin irritation

  TEWL is sensitive to skin irritation due to many different substances such as detergents or surfactants (Wilhelm et al. 1989; Effendy and Maibach 1995; Gabard 1991), all-trans retinoic acid (Gabard 1991; Effendy et al. 1996a), alpha-hydroxy acids such as glycolic acid (Effendy et al. 1995), newborn fecal enzymes (Andersen et al. 1994), or vitamin D derivatives (Effendy et al. 1996b; Fullerton and Serup 1997). Sodium lauryl sulfate is probably the most commonly used standard irritant in experimental dermatology. A recent guideline was published by the Standardization Group of the European Society of Contact Dermatitis about the standardization of experiments using this compound (Tupker et al. 1997). Measurement of TEWL may also be beneficial in experiments with animals or for comparison with human skin values (Fullerton and Serup 1997; Gendimenico et al. 1995; Gabard et al. 1995; Von Brenken et al. 1997). Differences may be encountered between various animal species as well as between animals and humans (Effendy et al. 1996b; Fullerton and Serup 1997; Von Brenken et al. 1997).
- Effects of UV irradiation

  Differences also are noticed between animals and humans considering the TEWL changes after an UV-B irradiation (Frödin et al. 1988; Haratake et al. 1997).
- Evaluation of topical products

  TEWL may be advantageously used for the investigation of some properties of topical products such as moisturizers (skin hydrating creams) after application on the skin. Measurement of the TEWL allows to characterize the changes of the product after application and the effect of different humectants contained in the product and also to precisely evaluate the occlusive properties of the formulation (Gabard 1994; Marti-Mestres et al. 1994).
- Therapeutic effects of topical products

  The TEWL also allows the evaluation of the therapeutic effect of topical products applied on diseased skin with a modified barrier function in animals and/or humans (Ghadially et al. 1992; Gabard et al. 1996; Lodén 1996, 1997; Mortz et al. 1997). The composition of the formulations may also be optimized with these experimental models (Zettersten et al. 1997). These experiments show on one side that contradictory results may be obtained if a diseased skin with modified barrier function is treated by a given formulation and on the other side that the obtained results on product efficacy may not be extrapolated in a straightforward manner from animals to humans.

4.2 Clinical Dermatology

Pinnagoda and Tupker (1995) published pertinent examples of improving medical care by the use of TEWL measurements in pathological situations:

- Various types of cutaneous inflammation.
- Follow-up of the course of atopic dermatitis (Aalto-Korte 1995; Seidenari and Giusti 1995): Aalto-Corte (1995) could show that the improvement of skin barrier function as measured by TEWL was accompanied by a decrease of the cutaneous absorption of hydrocortisone used for treatment.

– Psoriasis, different types of ichthyoses.
– Wound healing, regeneration of burned skin.
– Follow-up of newborn babies.
– Possibility of differentiating between an allergic or irritant reaction after patch testing (Giorgini et al. 1996).

This list remains succinct; the interested reader will report with benefit to the publication of Pinnagoda and Tupker (1995) where in-depth information are given about clinical applications of TEWL measurements. Obviously, some complications remain concerning a daily use of this technique in a hospital environment, the most important one being the necessity to conduct the measurements in a controlled and standardized environment.

5 Conclusions

The TEWL mirrors the integrity of the physiological barrier built up by the horny layer. Due to the availability of easy-to-use and precise equipments, the TEWL may now be easily measured. In that way, important information on skin water barrier may be gathered, concerning, for example, the behavior of topical products during development and use, differences between man and animals, etc. This information is pertinent, considering the fact that TEWL remains the most sensitive parameter for the detection of a cutaneous irritation. However, the obtained results are meaningful only if well-standardized measurement conditions are guaranteed. This remains an obstacle to an extended daily use.

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