MULTI-LOCATION CLINICAL TRIALS:

DO TEWL READINGS CHANGE WITH ALTITUDE?

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1. INTRODUCTION

With increasing globalisation, multi-location clinical trials of topical products are becoming more commonplace. In such trials, it is important to use instruments that are accurately calibrated, to ensure comparability at different locations. But even accurately calibrated instruments may perform differently at different locations, if their readings are affected by atmospheric pressure, as may be the case with TEWL instruments.

2. BACKGROUND

TEWL measurement methods all rely on evaporimetry, where TEWL is inferred from the water evaporation flux in the air immediately adjacent to the skin surface. All the commonly used methods (open-chamber, condenser-chamber & unventilated-chamber), involve the diffusion water vapour through air, from the skin surface to the sensor(s) and beyond. The associated mass diffusion coefficient, ***D***, is normally assumed to be a constant, but according to gas theory [1], it depends on temperature and pressure in accordance with equation (1).

$$D \propto \frac{T^{3/2}}{P} \qquad (1)$$

where ***T*** is absolute temperature and ***P*** is pressure. The effect on open-chamber TEWL measurements was first discussed by Nilsson [2]. He concluded that, at a given location, weather-related changes of atmospheric pressure could affect TEWL readings by as much as ±6%. This was deemed to be too small for further consideration.

Atmospheric pressure can also change with altitude, in accordance with the Barometric formula [3]

$$P \propto e^{-h/h_0} \qquad (2)$$

where ***h*** is altitude and h_0 is the scale height (~8400m). Altitude-related changes were not considered by Nilsson, but they can be significantly bigger. For example, open-chamber TEWL readings in New York (~sea level) and Denver (~1600m altitude) would differ, according to equations (1-2), by ~20%.

It is not clear whether closed-chamber instruments are affected by atmospheric pressure in the same way as open-chamber instruments. To find out, we performed identical in-vivo TEWL measurements at a number of geographic locations of differing altitudes with two closed-chamber instruments using different measurement principles.

3. MATERIALS AND METHODS

The calendar dates, geographic locations, altitudes above sea level and atmospheric pressures where the measurements were performed are presented in Table 1.

Table 1: Locations used in the Study			
Date (2015)	**Location**	**Altitude (m)**	**Pressure (hPa)**
17/09	London	80	997
19/09	Engelberg	1000	910
20/09	Adelboden	1355	870
21/09	Oerlikon	425	966
23/09	Arosa	1700	824
24/09	St Gallen	670	943
27/09	London	80	1027

Altitudes were determined from Google Maps. Atmospheric pressures were measured using a USB Precision Barometer (Dracal Technologies Inc, Canada) to an accuracy of ±1.5hPa.

TEWL was measured using one unventilated-chamber VapoMeter (Delfin Technologies Ltd, Finland) and one condenser-chamber AquaFlux (Biox Systems Ltd, England).

Figure 1: The two closed-chamber instruments used in the study. Left: Unventilated-chamber VapoMeter. Right: Condenser-chamber AquaFlux.

At each geographic location, volar forearm TEWL measurements were performed on a single elderly subject with each instrument on the four sites of the volar forearm shown in Figure 2.

Figure 2: The four sites of the volar forearm measured with each instrument at each geographic location during the study.

The following measurement protocol was used at each geographic location:-

1. Prepare the AquaFlux instrument for measurement.
2. Ensure that the ambient conditions conform to the TEWL measurement guidelines (temperature <22°C, RH < 60%) [4] and that the subject is well acclimatised.
3. Measure each site in quick succession (elbow to hand direction) using the AquaFlux instrument and inspect the measured flux curves for signs of sweat gland activity. Continue with acclimatisation or abandon the measurement session if there is any sign of sweating.
4. Measure each site in quick succession (elbow to hand direction) using the VapoMeter instrument. Repeat four times.
5. Measure each site in quick succession (elbow to hand direction) using the AquaFlux instrument. Repeat four times.

4. RESULTS

The four sites were found to have broadly similar barrier function, so it made sense to use the mean TEWL of all four skin sites and all four repeats (16 measurements/point) for the analysis presented in Figure 3. The trend lines were calculated using the weighted least-squares method, to take into account the standard deviations of the data points.

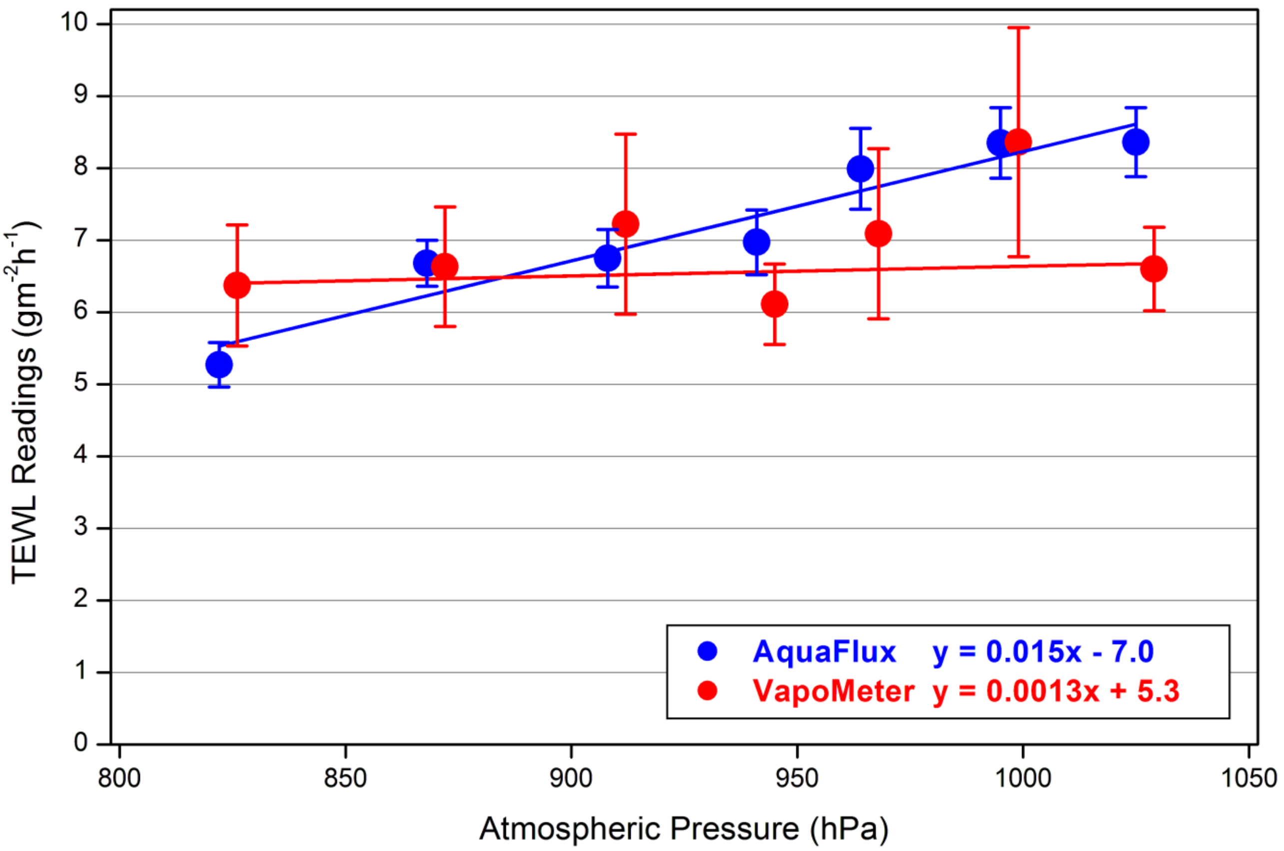

Figure 3: Dependence of mean TEWL on atmospheric pressure. Each point is an average of all four skin sites and all four repeats (16 measurements/point). The error bars are standard deviations that include both site variability and instrumental repeatability. Note that the red and blue points are offset by ±2hPa to avoid overlap.

In Figure 3, the AquaFlux measurements show a clear trend of increasing TEWL readings with increasing atmospheric pressure (gradient = $[150 \pm 22] \times 10^{-4}$ $gm^{-2}h^{-1}$/hPa). No pressure-dependent trend is apparent in the VapoMeter measurements (gradient = $[13 \pm 44] \times 10^{-4}$ $gm^{-2}h^{-1}$/hPa), although a weak pressure dependence cannot be ruled out, given the relatively large standard deviation of the gradient.

5. SUMMARY AND CONCLUSIONS

We found distinctly different responses of the two TEWL instruments used in this study to changes of atmospheric pressure. This could be due to the different measurement principles they use.

The condenser-chamber AquaFlux uses the steady-state diffusion gradient measurement principle based on Fick's first law of diffusion. This is the same as the open-chamber and a similar pressure dependence as given in equation (1) can be expected. Equations (1-2) can then be used to normalise measurements performed at different altitudes to standard sea-level atmospheric pressure.

The unstirred-chamber VapoMeter uses a non-steady-state time-rate-of-change measurement principle based on Fick's second law of diffusion. Pressure changes cause the diffusion transit times of water vapour from skin to sensor to change, but it appears that any effect on the TEWL readings of this instrument is small compared with its measurement uncertainties.

6. REFERENCES

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