THE EFFECT OF AMBIENT TEMPERATURE ON INSULIN PUMP FUNCTION.

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Background

Reduction in atmospheric pressure causes unintended insulin delivery from insulin pumps (1).

The change in insulin delivery is due to the physical properties of water and air. Air dissolves in water. The amount of air that dissolves in water is proportional to the atmospheric pressure [2]. Hence as the atmospheric pressure decreases, air comes out of solution displacing the insulin and causing unintended insulin delivery. This may become clinically significant in tightly controlled diabetic patients, particularly children and risks hypoglycaemia (1). Rapid reduction in atmospheric pressure occurs in aircraft ascent so may be frequently encountered by some patients using insulin pumps. If the patient is aware of the phenomenon, unintended insulin delivery from pumps can be eliminated by simple measures (1).

Having demonstrated the effects of atmospheric pressure reduction and insulin delivery, we questioned whether there may be other physical properties of water (such as temperature) that could influence insulin delivery from insulin pumps.

Insulin pump users frequently wear the pump very close to their skin (body skin temperature up to 37°C). Insulin is routinely stored in a refrigerator (4°C) as recommended by insulin manufacturers (3). Warm climate countries like Australia may experience high ambient temperatures sometimes reaching over 40°C. Insulin may not be warmed to room temperature before it inserted into the insulin pump cartridge and commenced as therapy.

The coefficient of thermal expansion of water states that as the temperature increases between 4°C an 40°C water expands (4). Henry's law involves temperature. As the temperature increases air comes out of solution (2). Charles's law states that the volume of a gas is proportional to the temperature (5). Hence if air bubbles were present, then they would expand as the temperature increased. This could displace insulin from an insulin pump.

Hence this raised the possibility that there could be unintended insulin delivery from a pump as insulin warmed within the cartridge. Insulin pump manufacturers recognize that temperature influences insulin delivery from insulin pumps (6).

Hypothesis and Aim

We hypothesized that increases in ambient temperature cause extra insulin delivery from insulin pumps by three mechanisms:

1. Expansion of insulin (water) as temperature increases (thermal expansion).
2. Formation of air bubbles in the insulin due to air coming out of solution as the temperature increases (Henry's Law).
3. Expansion of bubbles that were already present in the insulin cartridge (Charles's Law).

We studied the effects of increasing temperature on insulin pump delivery.

Methods

Because only mechanical equipment was used no ethics approval was sought.

Mathematical Modeling

The equation for volumetric thermal expansion of fluids used was:

$$\frac{\Delta V}{V} = \int_{T_4}^{T_{4+37}} \alpha\, v(T)\, dT$$

The coefficient of expansion of water (7) was defined as :

$$\alpha_V = \frac{1}{V}\left(\frac{\partial V}{\partial T}\right)_p$$

Although insulin solution is predominantly water, it is not distilled water. To model the effects of solutes in the insulin (electrolytes, protein), we used the coefficient of thermal expansion of 1% saline.

To model the thermal expansion of the insulin cartridge, with increasing temperature, the cartridge was assumed to be made of polypropylene (with a linear thermal expansion coefficient of 146-180 x 10-6) (8). In the modeling, the cartridge volume was compared if the linear coefficient of thermal expansion at 146 10^{-6}/°C or 180 x 10^{-6}/°C.

The circumference was calculated using C = 2πR.

The area of the circle was calculated using A = πR^2.

The volume was calculated using V = area X length.

Methods (continued)

The equation of linear thermal expansion used was:

$$\frac{\Delta L}{L} = \alpha_L \Delta T$$

The coefficient of linear expansion was defined as:

$$\alpha_L = \frac{1}{L}\frac{dL}{dT}$$

The amount of air that should come out of solution (and displace insulin) was calculated using Henry's law.

$$k_{\mathrm{H,cp}}(T) = k_{\mathrm{H,cp}}(T^{\ominus})\exp\left[C\left(\frac{1}{T} - \frac{1}{T^{\ominus}}\right)\right]$$

C used for oxygen was 1700 and for nitrogen was 1300. T is temperature in Kelvin.

Confirmation with cartridges

Forty Roche Spirit pump cartridges were loaded with aspart insulin and food dye at 4°C. Infusion sets were attached and the cannula fixed in a 100 microL per 10 cm microtubule. This procedure was performed in a refrigerator at 4°C to ensure no gain in temperature.

The cartridges were then placed in a water bath at 37°C. The tubing was kept at the same level as the cartridge.

Air bubble formation study (testing Henry's law)

Forty Roche Spirit cartridges and 20 ANIMAS 2020 cartridges were loaded with aspart insulin. Infusion sets were attached and the cannula fixed in a 100 microL per 10 cm microtubule. All cartridges were examined to ensure no air bubbles were present. This procedure was performed in a refrigerator at 4°C to ensure no gain in temperature.

The cartridges were then placed in a water bath at 37°C. The tubing was kept at the same level as the cartridge. Ten minutes after the insulin in the microtubule had stopped moving, the cartridges were examined for bubbles.

Results

Mathematical modeling of insulin delivery as temperature increases.

The volume change of the cartridge and the volume change of the solution are the temperature changed from 4 to 40°C was modeled.

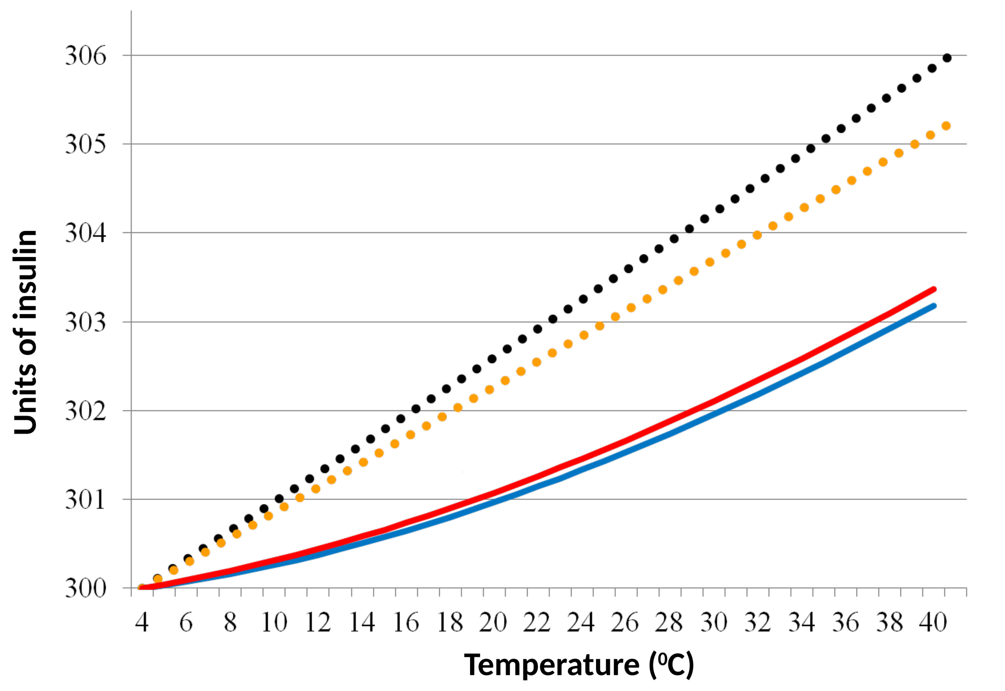

Figure 1: Modeling of heating an empty 3mL cartridge and 3mLs of distilled water or 1%saline from 4 to 40°C. The doted lines are the empty cartridge volume, with the black dots = linear coefficient of expansion (LCTE) of 180 X 10^{-6}, and the orange dotes LCTE = 146 X 10^{-6}. The solid blue line is 3mLs distilled water and the red solid line is 3mLs 1% saline.

Hence there was a differential between the volume of the cartridge and the volume of the solution.

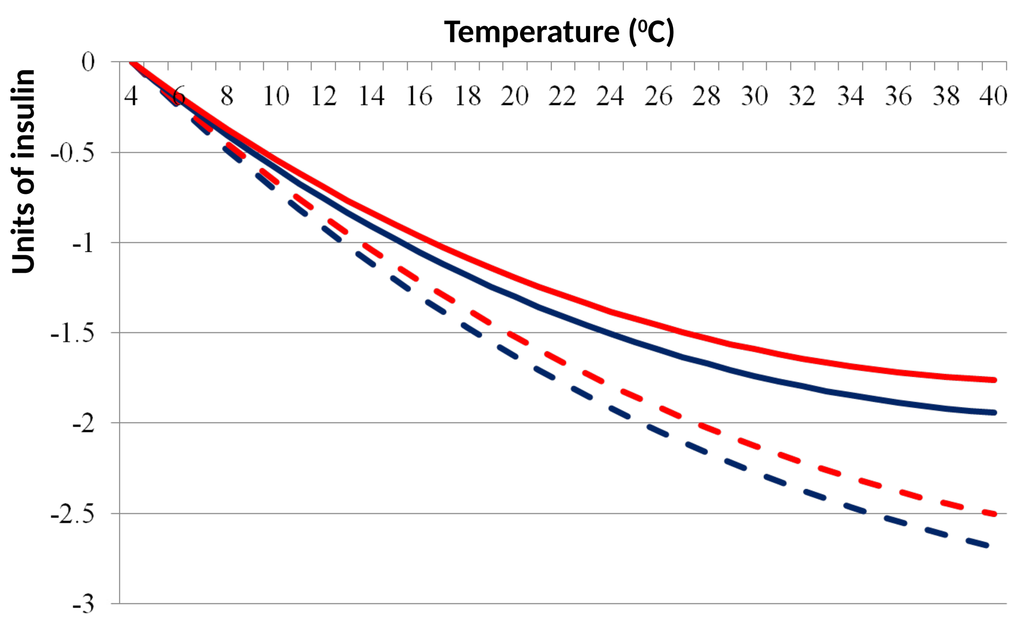

Figure 2: Modeling of heating a 3mL cartridge containing distilled water or 1% saline from 4 to 40°C. Blue lines are distilled water and red lines are 1% saline. The dashed lines LCTE = 180 X 10^{-6}, the solid line LCTE = 146 X 10^{-6}.

Confirmation with cartridges

When the cartridges were placed in the water, the insulin immediately retracted into the cartridge due to the cartridge expanding. As the insulin heated, it expanded but at no time did the insulin return to the starting point (i.e. there was a deficit).

Results (continued)

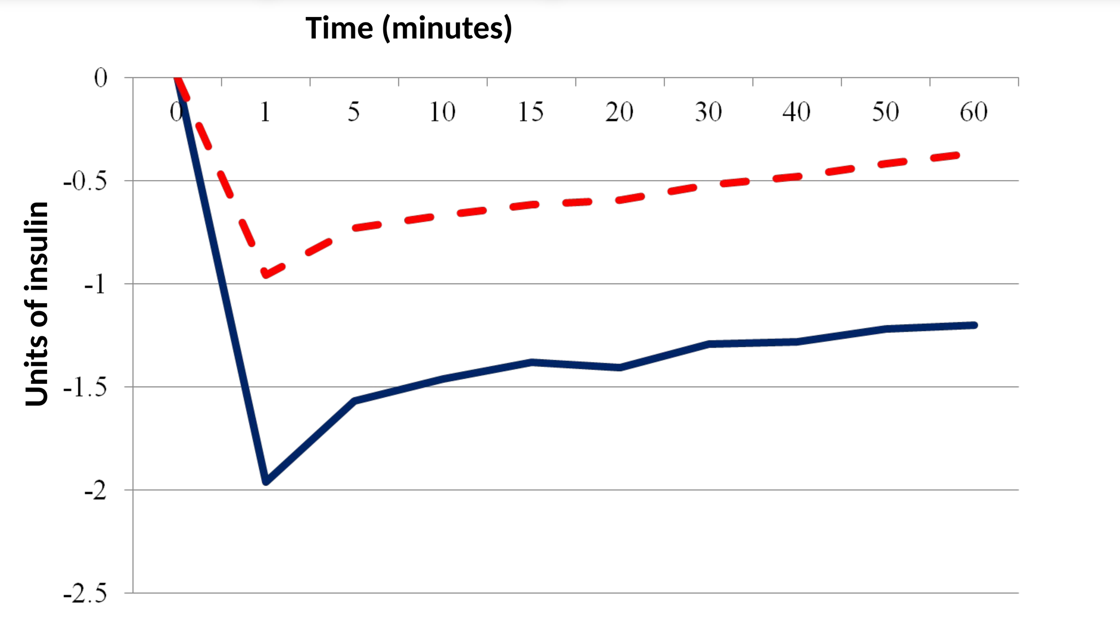

Figure 3: Cartridges for insulin pumps filled with aspart insulin and taken from a refrigerator (4°C) and placed in a water bath (37°C). Solid blue lines are Roche spirit cartridges (3 mL) and dashed red lines are ANIMAS 2020 cartridges (2 mL).

Air bubble formation study (testing Henry's law)

Bubbles developed and were clearly visible in all the cartridges during the warming phase.

Discussion / Conclusions

➢ **When ambient temperature increases, there is a deficit between the actual insulin and the volume of the cartridge which could potentially lead to a decrease in insulin delivery from insulin pumps as temperature increases.**

As the ambient temperature increases the polypropylene cartridge heats up first and expands. Hence, in the initial phase the insulin is sucked back into the cartridge. The heat is then transferred though the cartridge into the insulin and the insulin expands with the temperature change. However the expansion of the cartridge exceeds the expansion of the insulin resulting in an insulin deficit. Because a water bath was used the cartridge and insulin heated within one minute.

The deficit left in the 3mL insulin cartridge (Fig 3) was -1.2 units after 60 min but the modelling of polypropylene cartridge with LCTE = *146 X 10^{-6}* containing 1% saline solution suggested it should be -1.73 units. It is possible to put additives in the polypropylene to change the LCTE. The results we obtained suggest that the cartridge LCTE is *122.4 X 10^{-6}*

The expansion of the insulin was caused by thermal expansion and air coming out of solution formed bubbles that displace the insulin.

Further studies are in progress to define the curve of insulin delivery from actual insulin pumps during changes in ambient temperature.

Recommendations

All people using insulin pumps should be aware that:

➢ **If insulin is storied in a refrigerator**

Insulin should be warmed to room temperature before loading the insulin cartridge.

➢ **When wearing the insulin pump**

Insulin pumps should be worn inside clothing to maintain the insulin and cartridge temperature as constant as possible. Pumps should not be exposed to large temperature changes if possible.

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