Modifying the Baricity of Local Anesthetics for Spinal Anesthesia by Temperature Adjustment

Model Calculations

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Background: Although local anesthetics (LAs) are hyperbaric at room temperature, density drops within minutes after administration into the subarachnoid space. LAs become hypobaric and therefore may cranially ascend during spinal anesthesia in an uncontrolled manner. The authors hypothesized that temperature and density of LA solutions have a nonlinear relation that may be described by a polynomial equation, and that conversion of this equation may provide the temperature at which individual LAs are isobaric.

Methods: Density of cerebrospinal fluid was measured using a vibrating tube densitometer. Temperature-dependent density data were obtained from all LAs commonly used for spinal anesthesia, at least in triplicate at 5°C, 20°C, 30°C, and 37°C. The hypothesis was tested by fitting the obtained data into polynomial mathematical models allowing calculations of substance-specific isobaric temperatures.

Results: Cerebrospinal fluid at 37°C had a density of 1.000646 ± 0.0000086 g/ml. Three groups of local anesthetics with similar temperature (T), °C-dependent density (ρ) characteristics were identified: articaine and mepivacaine, ρ(T) = 1.008–5.36 E-06 T² (heavy LAs, hypobaric at body temperature); L-bupivacaine, ρ(T) = 1.0057–5.46 E-06 T² (intermediate LA, less hypobaric than saline); bupivacaine, ropivacaine, prilocaine, and lidocaine, ρ(T) = 1.0063–5.0 E-06 T² (light LAs, more hypobaric than saline). Isobaric temperatures (°C) were as follows: 5 mg/ml bupivacaine, 35.1; 5 mg/ml L-bupivacaine, 37.0; 5 mg/ml ropivacaine, 35.1; 20 mg/ml articaine, 39.4.

Conclusion: Sophisticated measurements and mathematical models now allow calculation of the ideal injection temperature of LAs and, thus, even better control of LA distribution within the cerebrospinal fluid. The given formulae allow the adaptation to subpopulations with varying cerebrospinal fluid density.

THE ratio of the density of local anesthetics (LAs) and cerebrospinal fluid (CSF), which is known as LA baricity, is one key determinant of LA distribution within the subarachnoid space.1-3 Although LAs are hyperbaric outside the body, in particular when stored at room temperatures or below until use, density and viscosity decrease within minutes after administration into the subarachnoid space. As a result, at first LAs sink within the CSF according to posturing as long as the temperature difference to CSF is high with a substance-specific velocity. Adaptation of LAs to CSF temperature decelerates sedimentation velocity until LAs become hypobaric and therefore again ascend. Besides the effect of warming LAs on pK values, which drop and consequently cause nonionized LA fraction rises,6 the temperature-dependent change in baricity has been shown to cause faster onset of block as well as higher maximum sensory levels of block during spinal anesthesia (SPA).5,7 In line with these findings, hypobaric solutions prolonged analgesia for hip replacement surgery,8 and CSF density was significantly positively correlated with peak level of sensory block.9 On the contrary, controllability of SPA extent is traditionally assured by addition of dextrose, leading to hyperbaricity of the LA solution.10 However, late cranial extent of SPA after posture change has also been reported using hyperbaric11 as well as isobaric solutions.12 In this regard, the volume of administered LAs seems to be of minor relevance.2,13

Measurements of CSF density have previously been performed by various authors,14-18 and the relationship to sex,15 pregnancy, or postmenopausal status18 is well established. A linear regression method to calculate the density of the admixture of glucose and opioids to LAs at a single temperature has been proposed by Hallworth et al.19 with the same method used in the current study and by Hare and Ngan20 with pyknometer measurements of lower precision. Previously described densities or baricities of LAs in part lack reliability because methods used are no longer up-to-date or temperature dependency was not considered. This issue was already addressed in the early 1990s by Horlocker and Wedel,1 who stated, “Comparison of densities [of LA] measured at 25°C to the density of CSF at 37°C is scientifically unsound.” However, linear relations of density from temperature were insinuated in former reports, although merely two temperatures were measured,16,21 thus not allowing conclusions on the curve shape. Unlike other fluids, the density of water and aqueous solutions is a nonlinear function of temperature (T); rather, it is described being a monotonic polynomial equation.22,23

We hypothesized that temperature and density of LA solutions have a nonlinear relation that may be described by a polynomial equation, and that conversion of this equation may provide the temperature at which individu-


Table 1. Density Formulae of Light Local Anesthetics

<table>
<thead>
<tr>
<th>Light LAs</th>
<th>Model Const.</th>
<th>Temperature Coefficient</th>
<th>Concentration Coefficient</th>
<th>Isobaric Temp., °C</th>
<th>Lower Limit, °C</th>
<th>Upper Limit, °C</th>
<th>$R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>$\rho(T) = 1.0064 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>2.5 mg/ml</td>
<td>$\rho(T) = 1.0051 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>3.75 mg/ml</td>
<td>$\rho(T) = 1.0068 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>5 mg/ml</td>
<td>$\rho(T) = 1.0067 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>2 mg/ml</td>
<td>$\rho(T) = 1.0067 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>5 mg/ml</td>
<td>$\rho(T) = 1.0068 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>10 mg/ml</td>
<td>$\rho(T) = 1.0068 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>$\rho(T) = 1.0064 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>10 mg/ml</td>
<td>$\rho(T) = 1.0064 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>15 mg/ml</td>
<td>$\rho(T) = 1.0064 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Prilocaine</td>
<td>$\rho(T) = 1.0061 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>10 mg/ml</td>
<td>$\rho(T) = 1.0061 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>15 mg/ml</td>
<td>$\rho(T) = 1.0061 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Light LAs</td>
<td>$\rho(T) = 1.0063 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Mathematical description of the density ($\rho, g/ml$) in light local anesthetics (LAs) in relation to temperature ($T, °C$) and concentration ($c, mg/ml$, regression models). Isobaric temperature ($°C$) and limits are calculated from cerebrospinal fluid density of men at 37°C and ± 3 SDs (upper/lower limit). Solutions are commercially available or were prepared with sterile saline (sal) or with distilled water (aq).

Materials and Methods

Our own CSF measurements were performed to obtain a reference quantity in the same methodologic setting for comparison with LA density data and to further calculate isobaric LA injection temperatures. After institutional review board approval (Ethikkommission der Medizinischen Fakultät Dresden, Germany, permission No. 168082004) and written informed consent, in seven male patients aged 45–60 yr undergoing SPA for transurethral resection of the prostate, the subarachnoid space was punctured at the L4–L5 interspace via a median approach using a 25-gauge Sprotte cannula. Before LA application, 2 ml free-flowing CSF without aspirating was collected for instant analysis. The densities of CSF and all LAs commercially available in Germany (tables 1–3) as well as that of saline were determined by means of a digital vibrating tube densitometer (DMA).

![Table 2. Density Formulae for Intermediate-weight Local Anesthetics](Image)

<table>
<thead>
<tr>
<th>Intermediate LAs</th>
<th>Model Const.</th>
<th>Temperature Coefficient</th>
<th>Concentration Coefficient</th>
<th>Isobaric Temp., °C</th>
<th>Lower Limit, °C</th>
<th>Upper Limit, °C</th>
<th>$R^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-bupivacaine</td>
<td>$\rho(T) = 1.0072 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>0.999</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>2.5 mg/ml</td>
<td>$\rho(T) = 1.0057 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>0.999</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>3.75 mg/ml</td>
<td>$\rho(T) = 1.0067 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>0.999</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>5 mg/ml</td>
<td>$\rho(T) = 1.0075 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>0.999</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>c mg/ml</td>
<td>$\rho(T) = 1.007 - 0.000005 \times T^2$</td>
<td>-0.000005</td>
<td>33.9</td>
<td>33.2</td>
<td>34.7</td>
<td>0.999</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

Mathematical description of the density ($\rho, g/ml$) in intermediate-weight local anesthetics (LAs) in relation to temperature ($T, °C$) and concentration ($c, mg/ml$, regression models). Isobaric temperature ($°C$) and limits are calculated from cerebrospinal fluid density of men at 37°C and ± 3 SDs (upper/lower limit). Solutions are commercially available or were prepared with sterile saline (sal) or with distilled water (aq).

*Anesthesiology, V 105, No 2, Aug 2006*
Table 3. Density Formulae of Heavy Local Anesthetics

<table>
<thead>
<tr>
<th>Model Const.</th>
<th>Temperature Coefficient</th>
<th>Concentration Coefficient</th>
<th>Isobaric Temp., °C</th>
<th>Lower Limit, °C</th>
<th>Upper Limit, °C</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper 2.5 mg/ml</td>
<td>( \rho(T) = 1.0143 - 0.000007 * T^2 )</td>
<td>44.2</td>
<td>43.7</td>
<td>44.6</td>
<td>0.984</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Hyper 5 mg/ml</td>
<td>( \rho(T) = 1.0207 - 0.000006 * T^2 )</td>
<td>57.8</td>
<td>57.4</td>
<td>58.2</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Articaine</td>
<td>10 mg/ml</td>
<td>( \rho(T) = 1.0076 - 0.000005 * T^2 )</td>
<td>37.3</td>
<td>36.6</td>
<td>38.0</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>15 mg/ml aq</td>
<td>( \rho(T) = 1.0063 - 0.000005 * T^2 )</td>
<td>33.6</td>
<td>32.9</td>
<td>34.4</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>15 mg/ml sal</td>
<td>( \rho(T) = 1.0080 - 0.000005 * T^2 )</td>
<td>38.4</td>
<td>37.7</td>
<td>39.0</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>20 mg/ml</td>
<td>( \rho(T) = 1.0094 - 0.000005 * T^2 )</td>
<td>39.4</td>
<td>38.7</td>
<td>40.0</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td>c mg/ml</td>
<td>( \mu(T,c) = 1.007 - 0.000005 * T^2 + 0.000075 * c )</td>
<td>0.991</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>10 mg/ml</td>
<td>( \rho(T) = 1.0078 - 0.000005 * T^2 )</td>
<td>37.8</td>
<td>37.1</td>
<td>38.5</td>
<td>1.000</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>15 mg/ml aq</td>
<td>( \rho(T) = 1.0063 - 0.000005 * T^2 )</td>
<td>33.6</td>
<td>32.9</td>
<td>34.4</td>
<td>0.999</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>15 mg/ml sal</td>
<td>( \rho(T) = 1.0080 - 0.000005 * T^2 )</td>
<td>38.4</td>
<td>37.7</td>
<td>39.0</td>
<td>0.999</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>20 mg/ml</td>
<td>( \rho(T) = 1.0085 - 0.000005 * T^2 )</td>
<td>39.6</td>
<td>39.0</td>
<td>40.3</td>
<td>0.999</td>
<td>0.000</td>
</tr>
<tr>
<td>c mg/ml</td>
<td>( \mu(T,c) = 1.007 - 0.000005 * T^2 + 0.000062 * c )</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy LAs</td>
<td>( \rho(T) = 1.008 - 0.00000536 * T^2 )</td>
<td>6 g/cm³</td>
<td>6 g/cm³</td>
<td>6 g/cm³</td>
<td>0.988</td>
<td>0.000</td>
<td></td>
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</table>

Mathematical description of the density (\( \mu, g/ml \)) in heavy local anesthetics (LAs) in relation to temperature (T, °C) and concentration (c, mg/ml, regression models). Isobaric temperature (°C) and limits are calculated from cerebrospinal fluid density of men at 37°C ± 3 SDs (upper/lower limit). Solutions are commercially available or were prepared with sterile saline (sal) or with distilled water (aq). Values in italics indicate isobaric range of temperature of hyperbaric bupivacaine far beyond body temperature, which is not clinically applicable. Heavy LAs formula not including hyperbaric bupivacaine.

Hyper = hyperbaric.

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observations and RSS is the residual sum of squares, which is directly proportional to $R^2$. Taking into account that all present models are based on the same number of observations and that they all solely contain the factor temperature, regardless of the number of (linear, quadratic, cubic, . . .) coefficients, the use of information criteria does not add much value to the simple consideration of $R^2$ for the estimation of individual model quality in the current data set.

For further generalization of the models, substance-specific formulae ($f(x,y) = ax^2 + by + c$) including temperature (°C) and concentration (mg/ml) were established. The latter were, as a matter of generalization and the inherent increase of residuals, of slightly lower model power, but still acceptable. Regarding Akaike’s criterion, these more complex models, in addition using the factor concentration, are inferior to the models calculated for the fixed combinations of substance and concentration.

To limit the formula load for clinical issues to a minimum, we consequently calculated models for each of the three identified subgroups of LAs, differentiating between light LAs (lighter than saline), intermediate LAs (between saline and CSF), and heavy LAs (in the range of CSF), regardless of their concentration.

The final step was then to calculate substance- and concentration-specific ideal injection temperatures ($T_{LAi}$) by combining formulae 1 and 2 ($\rho_{LA} = LA$ density; $T_{LA} = LA$ temperature), insinuating that LA density ideally ($\rho_{LAi}$) equals CSF density ($\rho_{CSF}$) and CSF having body temperature, to receive equation 3.

\[
\rho_{LA} = a \cdot T_{LA}^2 + b \tag{1}
\]

\[
\rho_{LAi} = \rho_{CSF} \tag{2}
\]

\[
\rho_{CSF} = a \cdot T_{LAi}^2 + b \tag{3}
\]

\[
T_{LAi} = \sqrt{\frac{\rho_{CSF} - b}{a}} \tag{4}
\]

Calculation of the ideal injection temperature by conversion of equation 3 to equation 4 is trivial.

Temperatures given in tables 1–3 are calculated from mean CSF density. The upper and lower limits are calculated from mean CSF density ± 3 SDs, respectively. By introduction of population-specific CSF density data,17,18 ideal injection temperatures may likewise be calculated for these patients.

### Results

The density (mean ± 1 SD) of CSF in the observed population ($n = 7$) was 1.000646 ± 0.000086 g/ml at 37°C; that of saline was 0.999748 ± 0.000001 g/ml. Temperature-dependent densities of local anesthetics can be found in figures 1–8. When defining the isobaric range according to Davis and King14 and Horlocker and Wedel,1 being mean CSF density ± 3 SDs, in all observed concentrations, bupivacaine, L-bupivacaine, ropivacaine, prilocaine, and lidocaine were found to be hypobaric at body temperature (figs. 1–3, 7, and 8). In contrast, 20 mg/ml articaine and 20 mg/ml mepivacaine remained slightly hyperbaric at body temperature (figs. 5 and 6). The only true isobaric LAs at 37°C were 10 and 15 mg/ml mepivacaine and 15 mg/ml articaine (figs. 5 and 6).

![Fig. 1. Effects of temperature and concentration on the density of bupivacaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits ($P$ and $R^2$ given in table 1). Bupivacaine, 5 and 2.5 mg/ml as commercially available solutions, 3.75 mg/ml (NaCl) diluted from 5 mg/ml with isotonic saline, 3.75 mg/ml (aq) diluted from 5 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) ($n = 7$) at 37°C; gray bar = 3-SD range.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931071/)

![Fig. 2. Effects of temperature and concentration on the density of levo (L)–bupivacaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits ($P$ and $R^2$ given in table 2). L-bupivacaine, 5 and 2.5 mg/ml as commercially available solutions, 3.75 mg/ml (NaCl) diluted from 5 mg/ml with isotonic saline, 3.75 mg/ml (aq) diluted from 5 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) ($n = 7$) at 37°C; gray bar = 3-SD range.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931071/)
Polynomial dependency of density from temperature was found in all LA preparations and could be described in simple quadratic mathematic models of satisfactory power (tables 1–3). Further, linear dependency of density from concentration was expectedly found (tables 1–3). In all cases, dilution with isotonic saline produced densities that fit into the characteristics of the commercially available preparations in the respective higher and lower concentrations. Dilution with distilled water, however, produced 0.001- to 0.003-g/ml lower densities at the same temperature and LA concentration, as compared with saline as diluent. Curve characteristics of 5 mg/ml bupivacaine and 5 mg/ml ropivacaine were identical (table 1).

Three groups of LAs with similar temperature-dependent density curve shape were identified: Bupivacaine, ropivacaine, prilocaine, and lidocaine were light LAs, being more hypobaric than saline at body temperature (table 1). L-bupivacaine had an intermediate position because its density lay between that of CSF and that of saline (table 2). Articaine and mepivacaine were heavy

Fig. 3. Effects of temperature and concentration on the density of ropivacaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits (P and R² given in table 1). Ropivacaine, 2, 5, 7.5, and 10 mg/ml as commercially available solutions, 5 mg/ml (aq) diluted from 10 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.

Fig. 4. Effects of temperature and concentration on the density of hyperbaric bupivacaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits (P and R² given in table 3). Note extended scale of y-axis versus all other figures. Hyperbaric (hyper) bupivacaine, 2.5 and 5 mg/ml as commercially available solutions. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.

Fig. 5. Effects of temperature and concentration on the density of articaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits (P and R² given in table 3). Articaine, 10 and 20 mg/ml as commercially available solutions, 15 mg/ml (NaCl) diluted from 20 mg/ml with isotonic saline, 15 mg/ml (aq) diluted from 20 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.

Fig. 6. Effects of temperature and concentration on the density of mepivacaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits (P and R² given in table 3). Mepivacaine, 10 and 20 mg/ml as commercially available solutions, 15 mg/ml (NaCl) diluted from 20 mg/ml with isotonic saline, 15 mg/ml (aq) diluted from 20 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.
Fig. 7. Effects of temperature and concentration on the density of lidocaine. Depicted are all measurements at least in triplicate per concentration at 5°, 20°, 30°, and 37°C and polynomial curve fits (P and \( R^2 \) given in table 1). Lidocaine, 10 and 20 mg/ml as commercially available solutions, 15 mg/ml (NaCl) diluted from 20 mg/ml with isotonic saline, 15 mg/ml (aq) diluted from 20 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.

Fig. 8. Effects of temperature and concentration on the density of prilocaine. Depicted are all measurements at least in triplicate per concentration at 5, 20, 30, and 37°C and polynomial curve fits (P and \( R^2 \) given in table 1). Prilocaine, 10 and 20 mg/ml as commercially available solutions, 15 mg/ml (NaCl) diluted from 20 mg/ml with isotonic saline, 15 mg/ml (aq) diluted from 20 mg/ml with distilled water. Horizontal line = cerebrospinal fluid (CSF) (n = 7) at 37°C; gray bar = 3-SD range.

**Discussion**

Baricity and the temperature of LAs are two closely related key factors affecting the cranial extent of SPA.\(^1\)\(^-\)\(^3\) Temperature adjustment of LAs for SPA to body temperature has been performed by our group and others, showing improvement of predictability of the SPA.\(^2\)\(^,\)\(^5\)\(^,\)\(^7\) Data from Higuchi et al.\(^9\) showing significant positive correlation between CSF density and peak level of sensory block indirectly support the clinical impact of LA density adjustment to CSF density.

A number of authors previously described densities of both LAs\(^1\)\(^,\)\(^10\)\(^,\)\(^16\)\(^,\)\(^19\)\(^-\)\(^21\) and CSF.\(^9\)\(^,\)\(^14\)\(^-\)\(^18\) However, a thorough high-precision description and modeling of the density-temperature relation of LAs is lacking. This is the first study to describe reliable polynomial models to predict LA densities over the clinical relevant range of temperature. Previously described densities or baricities of LAs in part lack reliability because methods are not contemporary\(^1\)\(^,\)\(^9\)\(^,\)\(^14\)\(^,\)\(^26\) or temperature dependency was not considered.\(^13\) In the current study, high-precision data were collected at least in triplicate at four defined temperature levels of each concentration of the respective LAs. Because previous studies gave LA densities without reporting temperature or merely at one or two temperature levels,\(^16\)\(^,\)\(^21\) conclusions on the curve shape could not been drawn, and the assumption of linear relation of temperature and density was speculative.

Unlike most fluids, density of water and likewise of aqueous solutions is a nonlinear function of temperature; rather, it is described as being a monotonic polynomial equation up to the fifth degree.\(^22\)\(^,\)\(^23\) This notion is a fundamental issue in oceanographic predictive models of ocean currents and meteorology. The polynomial nature of the dependence of LA density from temperature has not yet been addressed. If LA baricities defined as \( p_{LA}/p_{CSF} \) are compared, the problem of nonlinearity does not exist when corresponding LA and CSF densities are obtained at the same temperature level. By dividing LA density by CSF density, the commonly underlying polynomial factor temperature is then eliminated (divide the right side of equation 1 by the accordingly formulated \( p_{CSF} \)). However, because of complex protein interactions with density, viscosity, and pH value, it is not advisable to measure density of CSF outside a narrow range from body temperature. Therefore, the polynomial problem remains when comparing stationary CSF density (37°C) with temperature-variable LA density. Hence, it seemed most stringent to observe CSF density solely at body temperature as we usually find it in the clinical setting and face the problem of nonlinearity in the current work (figures 1–8).

In this regard, the cooling effect of the injected LA on CSF, when administered below body temperature, must be addressed.\(^26\)\(^,\)\(^27\) As a consequence of cooling CSF, the baricity of any given LA would slightly decrease until the baseline of CSF temperature is regained. This topic is rather difficult to predict and may not have the impact one would expect at first glance. First, CSF volume of patients is highly variable and individually merely not
predictable. Second, the subarachnoid space is not only a CSF-filled tube; rather, solid structures (cauda equina, nerve roots, blood-perfused arachnoidalia) with a far higher specific temperature capacity keep CSF temperature fairly stable. Despite this stable in vivo temperature condition of CSF, injection of LAs at room temperature showed slower onset of SPA and a lower maximum sensory level of block as compared with LAs injected at body temperature.

Polynomial equations of second or third degree for the investigated LA solutions were calculated by the authors (equations not shown). For clinical use, the accuracy of even more simple equations in the form \( \rho(T) = aT^2 + b \) is acceptable \( (R^2 > 0.998, P < 0.01; \text{tables 1–3}) \). Moreover, simple equations increase clinical utility and facilitate comparisons between the curve shapes of different LAs and are in accordance with straightforward model selection information criteria (e.g., Akaika’s criterion) as addressed in the Materials and Methods section. In this regard, the observed identical curve shapes of bupivacaine and ropivacaine in the 5-mg/ml concentration (figs. 1 and 3) may allow conclusions on comparable distribution of both LAs within the CSF with respect to the factor density.

In the current study, CSF density was obtained from male patients who were reported to have higher CSF density as compared with females (table 4). Therefore, mean isobaric temperature ranges will vary when using different CSF data. Keeping in mind the steep slope of the temperature-density curve around body temperature, slight subpopulation-specific variations of CSF density will not produce large variations in the isobaric temperature range. Computation of all given formulae (table 1–3) with the mean CSF data for the female patients reported by Schiffer et al. \( 17 \) (table 4) produced 0.2\(^\circ\)–0.6\(^\circ\)C higher isobaric LA temperatures.

The presented models derived from high-quality measurements of the variety of LAs within one standard methodologic data set may serve as reference formulæ that allow comparison of all substances in this regard. Further, conversion of the formula allows for calculation of the substance specific isobaric temperature, even in other populations of known CSF density. Direct clinical advice cannot be derived from the current laboratory investigation. In synopsis with in vivo data, \( 5,7 \) administration of LAs at their isobaric temperature may help to control one of the key factors of LA distribution in the CSF. Whether this concept in fact improves patient safety in terms of hemodynamic stability or even allows dose reductions of LA must be confirmed in further clinical studies.

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