Reports of Investigation

Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature

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Purpose: To determine the densities of cerebrospinal fluid (CSF) in patients for surgery under spinal anaesthesia. The densities of the CSF were compared with the densities of local anaesthestic solutions and their mixtures with commonly used spinal opioids.

Method: One ml of CSF was collected from 131 consecutive patients that consented to the study at the time of spinal anaesthesia. Densities were measured at 37°C in a Density Meter that displayed density to the fourth decimal point and was accurate to 0.00003 $g \cdot ml^{-1}$. The densities of a selection of spinal anaesthetic drugs were also measured.

Results: The mean CSF density in the study population was 1.00059 ± SD 0.00020. In men of all ages, the mean CSF density was 1.00067 ± 0.00018 $g \cdot ml^{-1}$; in postmenopausal women 1.00060 ± 0.00015 $g \cdot ml^{-1}$; in premenopausal non-pregnant women 1.00047 ± 0.00076 $g \cdot ml^{-1}$; and in pregnant women 1.00033 ± 0.00010 $g \cdot ml^{-1}$. There were differences between the CSF densities in pregnant women compared with men (P = 0.0001), postmenopausal women (P = 0.0001) and non-pregnant premenopausal women (P = 0.03). Local anaesthetic solutions that contain sugar (glucose or dextrose) were all hyperbaric. In the absence of sugar, all local anaesthetic solutions were hypobaric except for lidocaine CO_2 which was slightly hyperbaric. Opioids were all hypobaric except meperidine which was hyperbaric.

Conclusion: Pregnant women have slightly lower CSF densities than do men and postmenopausal women, and non-pregnant premanopausal women. In the absence of sugar all spinal anaesthetic solutions measured were hypobaric except for lidocaine CO_2 and meperidine, both of which were hyperbaric.

Objectif : Déterminer les densités du liquide céphalo-rachidien (LCR) chez des patients opérés sous rachianesthésie. Les densités du LCR ont été comparées à celles de solutions d'anesthésiques locaux pures ou comportant des opiacés couramment utilisés.

Méthodes : Un ml de LCR a été prélevé au moment de la rachianesthésie chez 131 patients consécutifs consentants. La densité a été mesurée au moyen d'un densimètre qui affiche les valeurs à la quatrième décimale avec une précision de 0,00003 $g \cdot ml^{-1}$. La densité d'une variété d'agents anesthésiques utilisés en rachi a aussi été mesurée.

Résultats : La densité moyenne du LCR dans la population étudiée était de 1,00059 ± ET 0,00020 $g \cdot ml^{-1}$. Chez les hommes de tout âge, la densité moyenne était de 1,00067 ± 0, 00018; chez les femmes ménopausées 1,00060 ± 0,00015; chez les femmes non ménopausées et non enceintes 1,00047 ± 0,00076 et chez les femmes enceintes 1,00033 ± 0,00010. Il y avait des différences dans la densité du LCR si l'on comparait les femmes enceintes et les homme (P = 0,0001), et les femmes ménopausées (P = 0,0001), et les femmes non ménopausées mais non enceintes (P = 0,03). Les solutions d'anesthésiques locaux qui contenaient du glucose étaient toutes hyperbares et en l'absence de sucre, elles étaient toutes hypobares, sauf pour la lidocaïne CO_2 qui était légèrement hyperbare. Les solutions d'opiacés étaient toutes hypobares sauf la mépéridine qui était hyperbare.

Conclusion : Les femmes enceintes ont une densité de LCR légèrement plus basse que les hommes, les femmes ménopausées et les femmes non ménopausées mais non enceintes. En l'absence de sucre, toutes les solutions anesthésiques évaluées étaient hypobares sauf la lidocaïne CO_2 et la mépéridine qui étaient hyperbares.

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THE distribution of local anaesthetic in spinal anaesthesia is determined by the baricity of the solution.[1,2] Baricity is the ratio of the density (mass/volume) of the local anaesthetic to the density of the cerebrospinal fluid (CSF). Thus, baricity influences local anaesthetic spread and block height since gravity causes hyperbaric solutions to flow downward in the CSF, whereas hypobaric solutions tend to rise. In contrast, gravity has no effect on the distribution of truly isobaric solutions. This is a fundamental principle in spinal anaesthesia yet there is a paucity of data on the density of CSF in patients presenting for surgery. Unfortunately, the few studies that incorporate CSF density measurements have limitations which include: small number of subjects,[3–5] patients with neurological abnormalities,[3] or geriatric and diabetic patients.[6]

The first report that accurately measured the specific gravity of CSF at 37°C utilised a Westphal Specific Gravity Balance.[3] The CSF density was then calculated, based on water density. Specific gravity is the ratio of the density of the solution to the density of water at a given temperature. Levin *et al.* determined the density of CSF in patients using the volumetric method.[4] This involved filling a pyknometer with the CSF. The pyknometer is a flask designed to contain a precise volume of fluid which can be equilibrated to 37°C in a water bath and then weighed to determine the density of the fluid within the flask.

Density varies inversely with temperature. The actual change in density with temperature cannot be predicted with different solutions. The temperature of local anaesthetic rapidly equilibrates with the core temperature of the CSF (37–38°C). In order to determine accurately the baricity that dictates the spread of local anaesthetic, the density of CSF and the density of the local anaesthetic must be measured at 37–38°C. In studies that measured the CSF at 37°C, the densities reported varied from 1.00021[5] to 1.003[6] $g \cdot ml^{-1}$. Various authors defined solutions with densities exceeding the 95%[4] or 99%[3] confidence limits of CSF density as hyperbaric, and densities below the limit as hypobaric.

Becker *et al.*[5] were the first to use the oscillometric technique which allowed them to measure densities at 37°C using volumes of less than 1 ml in 22 patients undergoing spinal anaesthesia. Richardson and Wissler[7] recently reported on the density of CSF in 44 pregnant and nonpregnant humans, measured at 37°C using an oscillometric method that reads density to the fifth decimal place. Horlocker and Wedel[8] measured the densities of various local anaesthetic at 37°C using the volumetric method.

The *purpose* of this study was to determine the density of CSF at 37°C in 131 patients presenting for surgery performed under spinal anaesthesia. In order to define the baricity of local anaesthetics, the same equipment was used to determine the densities of local anaesthetics and mixtures of local anaesthetics with narcotics that are commonly used in our practice. The densities of potential neuraxial drugs were also measured.

Methods

Following institutional approval and signed informed consent, CSF samples were collected at the time of spinal anaesthesia from 131 consecutive patients scheduled for elective surgery. One millilitre of clear, spontaneously flowing CSF was collected from each patient into sterile 10 ml test tubes and sealed with a rubber stopper. The CSF sample was analysed within 15 min of collection.

The CSF density was measured in the Anton Paar DMA 48 Density Meter after equilibration to 37°C. This equipment has a measuring range from 0–3 $g \cdot ml^{-1}$ with a precision of $\pm 3 \times 10^{-5}$ $g \cdot ml^{-1}$ and displayed density specified as $\pm$ 0.0001 $g \cdot ml^{-1}$. The microcomputer-controlled DMA 48 Density Meter determines density of fluids with the use of the oscillating technique. The sample is injected into the constant volume glass tube. Electromagnetic excitation of the glass tube produces an undampened oscillation. When the temperature is held constant, the period of oscillation varies with the density of the sample. The built-in thermostat provided constant temperature of 37°C with the precision of ± 0.01°C. The DMA 48 calibration was checked periodically using pure distilled water and remained stable during the study recording the density of H_2O at 37°C as 0.9933 $g \cdot ml^{-1}$, the same as in the reference sources provided by the manufacturer.

The densities of spinal anaesthetic solutions were measured at 37°C using the same technique. The choice of local anaesthetics and their mixtures with other medications was based on current clinical practice in our institution. We measured the density of the following local anaesthetics and their additives: lidocaine 5% + 75 $mg \cdot ml^{-1}$ glucose, bupivacaine 0.75% + 82.5 mg/ml^{-1} dextrose, lidocaine 2%, lidocaine 2% CO_2, bupivacaine 0.5%, ropivacaine 0.5%, tetracaine, fentanyl, sufentanil, meperidine, morphine-EPD (preservative free morphine), epinephrine and normal saline. In addition, medications that investigators have used intrathecally were also measured. These included midazolam, ketorolac, naloxone and droperidol.

The CSF and blood glucose concentrations were analysed by the hexokinase method (Gluco-quant®, Boehringer Mannheim): CSF protein was assayed using

the Pyrogallol Red-molybdate complex reaction (Quan Ttest Red Total Protein Assay System, Quantimetrix Corporation).

Patient demographic data, mean CSF densities, the variability of measurements (SD) and 95% confidence limits of the mean CSF density for the patient population were computed. Comparisons of CSF densities among the groups of patients in our study were made using a General Linear Model (GLM) analysis of variance (ANOVA) for unbalanced models. The Games-Howel multiple comparison test which is the procedure of choice for cells having unequal sample sizes (*ns*), as well as least squares pairwise contrasts were used where appropriate to compare intergroup differences. As well, linear regression modeling was used to examine the possible effects of various biochemical variables on CSF density. Values were expressed as mean ± SD except where indicated. $P < 0.05$ was considered to be statistically significant.

Results

In the 131 patients studied there were 74 men and 57 women. Age ranged from 18 to 96 yr, mean age 56.8 yr; mean weight was 74.1 ± 15.4 kg; mean height was 168.6 ± 9.98 cm. Among the women, there were 28 postmenopausal, 7 premenopausal non-pregnant and 22 pregnant patients. All pregnant patients were at term gestation scheduled for the elective Caesarean section.

Mean CSF densities, standard deviations of measurements and 95% confidence limits of the mean CSF density in each group of patients are presented in Table I. The mean CSF density was 1.00059 ± 0.00020 g·ml^{-1}. In men of all ages, the mean CSF density was 1.00067 ± 0.00018 g·ml^{-1}. In postmenopausal women, 1.00060 ± 0.00015 g·ml^{-1}. There was no difference between men and postmenopausal women. Statistically significant differences were observed in the CSF densities in pregnant women (mean CSF density = 1.00033 ± 0.00010 g·ml^{-1}) compared with men ($P = 0.0001$) and postmenopausal women ($P = 0.0001$) as well as premenopausal non-pregnant women (mean CSF density = 1.00047 ± 0.00076 g·ml^{-1} ($P = 0.03$). In men and non-pregnant women, CSF density did not vary with age.

Eight samples were analysed for CSF glucose and CSF protein concentration. There was a low non-significant correlation (r = .277) between CSF glucose concentration and CSF density. On the other hand there was a correlation ($P = .008$; r = .89) between the CSF protein concentration and the CSF density. Thus an increase in CSF protein appeared to be related to an increase in CSF density.

Pregnant women were excluded in the analysis of patients with diabetes and neurological disorder to avoid confounding data. The CSF density in diabetic patients (n = 12) was also compared with that in non-diabetic patients (n = 97). There was no difference in the CSF densities between these two groups. Forty patients had blood glucose as part of their pre-operative assessment. In these patients, there was a low non-significant correlation (r = 0.222) between their blood glucose concentration and CSF density.

There were seven patients with neuorological disorder. The mean CSF density in this group of patients was 1.00073 ± 0.00026 g·ml^{-1} was comparable with the mean CSF density (1.00064 ± 0.00016 g·ml^{-1}) in patients with no neurological disorder (n = 102). The diagnoses of patients with neurological disorders included: one pituitary tumour, two quadraplegia, one Parkinson's disease, one dementia, one seizure disorder, one stroke.

Table II lists the densities of the local anaesthetics, opioids, saline and water. Mathematically, hyperbaricity is assumed if the density of the solution exceeds the upper 99% confidence limit of the CSF density (1.00099). The solution is hypobaric when the density is below the lower confidence limit (1.00019) of the CSF density. Both lidocaine and bupivacaine solutions containing glucose and dextrose respectively were clearly hyperbaric. Without sugar, all local anaesthetics studied except lidocaine CO_2 were hypobaric according to the above definition. The hypobaric local anaesthetics

TABLE I Patient numbers, age, and mean CSF density with upper and lower 95% confidence limits

Group	*No. of patients*	*Age*	*CSF density*	*CSF density 95% confidence limits (lower - upper)*
All patients	131	56.8 ± 19.3	1.00059 ± 0.00020	1.00019–1.00099
men	74	61.8 ± 16.1	1.00067 ± 0.00018	1.00031–1.00103
postmenopausal	29	70.8 ± 10.3	1.00060 ± 0.00015	1.00030–1.00090
premenopausal	8	35.1 ± 7.2	1.00047 ± 0.00008	1.00031–1.00063
pregnant	22	29.7 ± 6.1	1.00033 ± 0.00010	1.00013–1.00053

Values are mean ± SD

TABLE II Density at 37°C of individual solutions

Drugs	*Concentration*	*Source*	*Density g/ml*
Local anaesthetics			
Bupivacaine	0.25%, 2.5 mg·ml^{-1}	Astra	0.9990
Bupivacaine	0.5%, 5 mg·ml^{-1}	Astra	0.9993
Bupivacaine	0.5%, 5 mg·ml^{-1}	Sanofi-Winthrop	0.9993
Bupivacaine + dextrose	0.75%, 7.5 mg·ml^{-1}	Sanofi Winthrop	1.0247
Ropivacaine	5 mg·ml^{-1}	Astra	0.9993
Xylocard®*	20 mg·ml^{-1}	Astra	0.9997
Lidocaine	2%, 20 mg·ml^{-1}	Astra	0.9999
Lidocaine CO_2	2%, 20 mg·ml^{-1}	Astra	1.0010
Tetracaine in NS†‡	0.5 mg·ml^{-1}	Sanofi-Winthrop	0.9995
Tetracaine in NS†	1 mg·ml^{-1}	Sanofi-Winthrop	0.9995
Tetracaine in NS†	2 mg·ml^{-1}	Sanofi-Winthrop	0.9997
Tetracaine in 10% dextrose	5 mg·ml^{-1}	Sanofi-Winthrop	1.0273
Opioids			
Fentanyl	50 µg·ml^{-1}	Abbott, Toronto	0.9932
Sufentanil	50 µg·ml^{-1}	Janssen	0.9933
Morphine-EPD	1 mg·ml^{-1}	Abbott,	
Meperidine	100 mg·ml^{-1}	Abbott, Toronto	1.0083
Others			
Ketorolac[16]	30 mg·ml^{-1}	Hoffman La Roche	0.9884
H_2O no additives		Abbott, St.Laurent	0.9933
Droperidol[17]	2.5 mg·ml^{-1}	Sabex	0.9944
NS,† preservative free	0.9%, 9 mg·ml^{-1}	Astra	0.9995
Midazolam[18]	1 mg·ml^{-1}	Roche	0.9997
Naloxone[19]	0.4 mg·ml^{-1}	Sabex	0.9997
Epinephrine	1:1000, 1 mg·ml^{-1}	Abbott, Montreal	1.0005
Dextrose	10%, 100 mg·ml^{-1}	Abbott, Montreal	1.0268

*contains NaCl 6 mg·ml^{-1}

†NS = normal saline

studied included lidocaine 2% in two different formats (Xylocard® and preservative free polyampules by Astra), bupivacaine 0.5%, bupivacaine 0.25%, ropivacaine 0.5%, and lyophilised tetracaine dissolved in preservative free saline to final concentrations of 2 mg·ml^{-1}, 1 mg·ml^{-1} and 0.5 mg·ml^{-1}. The density of lidocaine CO_2 was 1.0010 g·ml^{-1}, marginally higher than the upper confidence limit of the mean CSF.

Opioids commonly used in spinal anaesthesia at our institution included 50 µg/ml sufentanil, 50 µg·ml^{-1} fentanyl, 100 mg·ml^{-1} meperidine and morphine-EPD (preservative free morphine mg·ml^{-1}). Meperidine was hyperbaric (density = 1.0083 g·ml^{-1}) and all the other opioids studied were hypobaric. The density of epinephrine 1:1000 (1 mg·ml^{-1}) was isobaric at 1.0005 g·ml^{-1}. We have also measured the densities of substances that have been reported to be administered into cerebrospinal fluid, although most of them are not currently used clinically. These include ketorolac, naloxone, midazolam and droperidol. The specific source of each drug was included in Table II as there may be differences in the density of the same drug depending on the buffer used by different companies.

Figure 1 illustrates the densities and baricities of some representative spinal anaesthetic solutions.

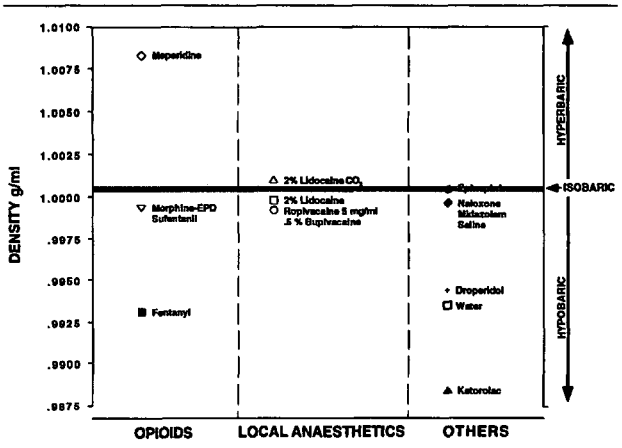

FIGURE Densities and baricities of spinal anaesthetic solutions at 37°C. Grey horizontal bar represents 95% confidence limits of CSF density for study population. Solutions containing dextrose or glucose have been excluded.

The densities of local anaesthetics and their mixtures with opioids in the doses commonly used in our institution are presented in Table III. The hyperbaric local anaesthetic solutions remained hyperbaric with the addition of any opioids or epinephrine. The amount of

TABLE III Densities of local anaesthetic mixtures at 37°C ($g \cdot ml^{-1}$)

Additives/ Local anaesthetics	*5% lidocaine**	*0.75% bupivacaine†*	*0.5% bupivacaine*	*0.5% bupivacaine*
	1.2 ml	1.5 ml	2 ml	3 ml
None	1.0249	1.0247	0.9993	0.9993
Fentanyl 25 μg, 0.5 ml	1.0159	1.0170	0.9979	0.9985
(+ Epi 0.2 mg, 0.2 ml)	(1.0138)	(1.0153)	(0.9982)	(0.9985)
Sufentanil 10 μg, 0.2 ml	1.0199	1.0211	0.9987	0.9989
(+ Epi 0.2 mg, 0.2 ml)	(1.0181)	(1.0190)	(0.9988)	(0.9990)
Morphine-EPD 0.3 mg, 0.3 ml	1.0198	1.0203	0.9992	0.9993
(+ Epi 0.2 mg, 0.2 ml)	(1.0177)	(1.0188)	(0.9994)	(0.9994)
Meperidine 20 mg, 0.2 ml	1.0225	1.0226	1.0000	0.9998
(+ Epi 0.2 mg, 0.2 ml)	(1.0198)	(1.0206)	(1.0001)	(0.9999)

*glucose 75 $mg \cdot ml^{-1}$
†dextrose 82.5 $mg \cdot ml^{-1}$

opioid and epinephrine that is mixed with a specific volume of local anaesthetic was chosen to reflect the most common mixtures used at our institution. When meperidine was added to hypobaric local anaesthetics, the density was increased slightly but not enough to bring the final density of the mixture to within the lower confidence limit of the CSF density. Thus the final solution remained hypobaric. Adding morphine-EPD to local anaesthetics resulted in minimal change in the final density of the mixture. Both sufentanil and fentanyl reduced the density of the final local anaesthetic-opioid mixture.

One patient had a continuous spinal anaesthetic. The CSF density was measured before and after injection of 1 ml bupivacaine 0.5% with a density of 0.9994 $g \cdot ml^{-1}$. The CSF density was not altered within one minute of injection: pre injection density was 1.0006 $g \cdot ml^{-1}$, and post injection was 1.0006 $g \cdot ml^{-1}$.

Discussion

This study measured the CSF densities in 131 consecutive patients presenting for surgery under spinal anaesthesia at 37°C using a Density Meter that was accurate to 0.00003 $g \cdot ml^{-1}$. The mean CSF density was 1.00059 ± 0.00020 $g \cdot ml^{-1}$.

The population of patients studied reflected the population typically encountered in our anaesthesia practice. The larger number (131) of patients studied allowed us to make some observations not previously reported in the literature.

Pregnant women had the lowest mean CSF density. The CSF density of non-pregnant women was similar to that of men of all ages. The mean CSF densities in this study were consistent with those reported by Richardson and Wissler[7]: pregnant women (n = 6) 1.00030 ± 0.00004 $g \cdot ml^{-1}$, premenopausal women (n = 6) 1.00049 ± 0.00004 $g \cdot ml^{-1}$, men (n = 10) 1.00070 ± 0.00018 $g \cdot ml^{-1}$.

Hormonal changes may be responsible for changes in CSF density in pregnant women. During pregnancy when the production of oestrogen and progesterone is highest, the CSF density appears to be at its lowest.

By definition, when the baricity of a solution is 1.0000, the solution is isobaric; >1.0000 is hyperbaric and <1.0000 is hypobaric. Since CSF density can vary in individuals, the baricity of any given solution will also vary. Thus, when reporting on spinal anaesthetic solutions, densities provide more useful information than baricities. Some authors have suggested that the solutions used for spinal anaesthesia are considered hypobaric when their density is less then the upper confidence limits of human CSF density, and hyperbaric when their density is below the lower confidence limits of human CSF density. This would appear to be mathematically correct.

However, the physical behaviour of the injectate may also depend on a number of different properties. How different does the density have to be to behave consistently as non-isobaric? In the patient with the continuous spinal, CSF density immediately following injection of 1 ml bupivacaine 0.5% was measured. There was no change in CSF density before and after the injection. Obviously, this finding needs to be confirmed in a larger study. Davis and King[9] found that 12 ml tetracaine injected at room temperature, resulted in a greater immediate decrease in the CSF temperature (6–8°C) than 2.4 ml (2–3°C). Spinal anaesthetic solutions may equilibrate with CSF density in a manner similar to the temperature change. If this is the case, then the volume of the injectate may modify its final density. Yet clinically, volume has not been found to be a determinant of block height, which is influenced by baricity of the spinal anaesthetic solution.

At 22°C, the injectate has a higher density than at 37°C. How the transition from room temperature to body temperature during the first few minutes of injection influences the distribution of the spinal anaesthetic is unclear. Rapid equilibration is not observed clinically with very hyperbaric solutions. This phenomenon is illustrated in the feasibility of a "saddle block" using hyperbaric solutions in the sitting position. Fortunately, the effect of hypobaric solutions is less dramatic and they seldom "float" to cervical levels. The critical minimum density difference that clinically defines hypobaricity and hyperbaricity is unknown.

This and previous studies[7,8] found lidocaine 2% to be numerically hypobaric. Interestingly, Bodily *et al.*[10] noted that lidocaine 2% as supplied by Astra behaved as an isobaric solution under clinical conditions. Even upon dilution of the lidocaine 2% with water to 1% solution, they still found that the hypobaric behaviour was unreliable. Only lidocaine 0.5% was found to form a clinically hypobaric solution.

Bupivacaine is considered isobaric by most practicing anaesthetists. Nevertheless, this study as well as others[11] demonstated that bupivacaine was hypobaric. To some extent bupivacaine injected at L_{2-3} or L_{3-4} interspace "floats" to effect a sensory block to T_6. This same concept applies to the "hypobaric" solution of lidocaine 1% with 25 μg fentanyl that results in a T_8 sensory block.[12]

There was no correlation between CSF or blood glucose concentration and CSF density. Since CSF glucose concentration varies with blood glucose concentration, this finding is consistent with Döbler and Nolte's[6] study who found no difference between CSF densities of diabetic and non-diabetic patients.

There was a positive correlation between CSF protein concentration and CSF density. The CSF protein can be elevated in inflammatory disorders, tumours and haemorrhage or infarction of the brain and meninges.[13] The density of the CSF in these patients can be predicted to be higher than the normal population. This was in contrast to an earlier report[3] that CSF protein did not affect CSF density.

The densities of the local anaesthetics and their mixtures were consistent with the findings of Horlocker and Wedel[8] who determined the densities using the pyknometer, as well as the results using the ocsillometric method.[14,15] These authors did not include lidocaine CO_2, meperidine, ketorolac, naloxone and midazolam in their studies.

To summarise, pregnant women had a slightly lower CSF density than the general population. Diabetes was not correlated with any change in CSF density. Certain disorders that cause elevation in CSF protein may also cause elevation in the CSF density. All local anaesthetic solutions tested were hypobaric except lidocaine CO_2 which was slightly hyperbaric. Local anaesthetics with dextrose or glucose were hyperbaric. All opioids tested were also hypobaric except for meperidine which was slightly hyperbaric. The addition of opiods to local anaesthetic solutions did not alter their relative baricity.

In conclusion, for an understanding of the baricity of spinal anaesthetics, it is important to know the CSF density at 37°C, taking into account interindividual and subpopulation variability. The density of the spinal anaesthetic solution should then be interpreted in light of the actual CSF density. The mathematical baricity is important to serve as the starting point in determining the distribution of the spinal anaesthetic solution. Additional factors contribute to its clinical behaviour: equilibration of the anaesthetic solution from room temperature to body temperature, and dilution with the CSF. Densities of spinal anaesthetic solutions must be accurately determined and then interpreted in the context of clinical findings.

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