

## Improved Statistical Methods for Quantal Assay

*To the Editor:*—This letter will argue that a recent report in ANESTHESIOLOGY would have been improved by different statistical methods; this letter is not a criticism of other research methods in the report. Ginosar *et al.*<sup>1</sup> reported a dose-response study of intrathecal hyperbaric bupivacaine (with adjuvant intrathecal opioids) administered for cesarean delivery in patients having a combined spinal-epidural technique. Seven groups of parturients—six patients per group—were randomly assigned to linearly spaced doses of bupivacaine (6, 7, 8, 9, 10, 11, or 12 mg). Success of the block (binary yes/no) was declared at 10 min after administration if a bilateral T6 pinprick sensory level existed (success<sub>induction</sub>); success<sub>operation</sub> was recorded if surgery proceeded without administration of any supplemental epidural local anesthetics. The observed response rates with increasing dose were success<sub>induction</sub> (3/6, 2/6, 6/6, 6/6, 6/6, 6/6) and success<sub>operation</sub> (1/6, 2/6, 4/6, 3/6, 6/6, 6/6, 6/6). Ginosar *et al.* used a version of the Hill equation (also known as the quantal sigmoid Emax model) to relate probability of success to dose of bupivacaine with two parameters,  $\gamma$  and dose<sub>50</sub>:

$$\text{Probability}\{\text{success} = \text{yes}\} = \frac{\text{dose}^\gamma}{\text{dose}^\gamma_{50} + \text{dose}^\gamma}$$

This was further described as logistic regression analysis of naïve-pooled data (one observation per patient) using Laplacian estimation routines of NONMEM (version V) statistical software (NONMEM Project Group, University of California, San Francisco, CA). Estimates of ED<sub>50</sub> with SEs were reported for success<sub>induction</sub> (6.7 ± 0.6 mg) and success<sub>operation</sub> (7.6 ± 0.4 mg); point estimates of ED<sub>95</sub> without standard errors were also reported (11.0 and 11.2 mg, respectively).

The community of statisticians has produced an extensive repertoire of methods for the analysis of quantal response data.<sup>2</sup> It is usually assumed that each individual of the relevant population has a dose tolerance or threshold for the particular substance being tested; a descriptive model characterizes the distribution of tolerances. It is possible, but not necessary, to use a logarithmic dose transformation. Assuming large sample properties, sigmoidicity, symmetry, and homoscedasticity, the most common simple model is called the logit or logistic regression:

$$\text{Probability}\{\text{success} = \text{yes}\} = \frac{1}{\exp^{-(\alpha + \beta \text{dose})} + 1},$$

where  $\alpha$  and  $\beta$  are location and scale parameters. Further, assuming a logistic probability density function, maximum likelihood estimation routines for  $\alpha$  and  $\beta$  by iteratively reweighted linear regression are available in most statistical software packages; using the  $\delta$  method, ED<sub>x</sub> with standard errors may be estimated for any  $x$  (0 <  $x$  < 100). The ED<sub>50</sub> represents the median value of the distribution of tolerances in the population. Counts for success and failure being available in their figure 1, the data of Ginosar *et al.*<sup>1</sup> can be reanalyzed assuming linear spacing of doses. Using the open software R statistical computing and graphics package\* (version 1.8.1) with the base and MASS libraries, the estimates for success<sub>induction</sub> are ED<sub>50</sub> (6.5 ± 0.4 mg) and ED<sub>95</sub> (8.6 ± 0.7 mg); the estimates for success<sub>operation</sub> are ED<sub>50</sub> (7.7 ± 0.4 mg) and ED<sub>95</sub> (10.6 ± 0.9 mg). The poor precision of the ED<sub>95</sub> estimates is apparent; the 95% confidence interval for success<sub>induction</sub> is 7.2-10.0 mg and for success<sub>operation</sub> is 8.8-12.4 mg.

Objections to the statistical methods can be briefly summarized. First, the Hill equation originated in studies of multiple ligand binding to allosteric proteins, in particular hemoglobin, the exponent  $\gamma$  (a slope parameter) being interpreted in a mechanistic way to reflect the cooperativity (interaction of ligands) in binding. In quantal assay, the  $\gamma$  parameter is sometimes described as the steepness of the probability of effect curve for an individual patient.<sup>3</sup> The complexity of general and spinal anesthesia allow considerable skepticism that the single parameter  $\gamma$  can have any deterministic/mechanistic interpretation. The more conservative approach is to consider any slope estimate of the anesthetic dose-response curve as purely descriptive of the distribution of thresholds in the patient population.

Second, as an extension of concepts developed in the mixed effects modeling of population pharmacokinetic data (multiple observations per subject), it has been argued that mixed effects modeling can be used on single response data to estimate an intraindividual and an interindividual variance.<sup>4</sup> However, a fundamental flaw was demonstrated in assumptions for such methods<sup>5</sup>: Data with only one observation per subject cannot be used to estimate an intraindividual variance. Thus, the nomenclature “naïve-pooled data,” commonly used in population pharmacokinetic modeling, is an incorrect description of the data structure in this experiment.

Third, the NONMEM statistical package is one of the prominent software tools developed for mixed effects modeling. Mathematical calculations within NONMEM such as Laplacian estimation are extremely complex, involving many assumptions and approximations; there is no consensus about the optimal estimation routines for mixed effects software.<sup>6</sup> Standard logistic regression software uses commonly accepted routines that allow the estimation of confidence intervals for arbitrary ED<sub>x</sub>, missing in the NONMEM output. It should be emphasized that even standard logistic regression analysis gives less precision for ED<sub>x</sub> values at the upper and lower edges of the sigmoid curve.

Fourth, simple algebraic manipulation shows that the quantal sigmoid Emax model can be rewritten in a logistic format:

$$\text{Probability}\{\text{success} = \text{yes}\} = \frac{1}{\exp^{-(-\gamma \ln(\text{dose}_{50}) + \gamma \ln(\text{dose}))} + 1} \Rightarrow \gamma = \beta; \ln(\text{dose}_{50}) = -\frac{\alpha}{\beta}$$

This restatement reveals that the quantal sigmoid Emax model enforces a logarithmic transformation of dose. Such a transformation may or may not be desirable. The standard logistic model leaves this choice to the modeler. In this experiment, bupivacaine doses were linearly spaced, and a logarithmic transform seems unnecessary. However, using a logarithmic dose transformation, the logistic regression estimates (with 95% confidence intervals) are ED<sub>50</sub> (6.5 [5.8-7.3] mg) and ED<sub>95</sub> (8.7 [7.1-10.5] mg) for success<sub>induction</sub> and ED<sub>50</sub> (7.6 [6.8-8.5] mg) and ED<sub>95</sub> (11.0 [8.8-13.6] mg) for success<sub>operation</sub>. The NONMEM estimate for the ED<sub>95</sub> of success<sub>induction</sub> is 11.0 mg, a value extremely discordant with the observed response rates (fig. 1, Ginosar *et al.*<sup>1</sup>); standard logistic regression gives estimates (linear dose, 8.6 mg; logarithmic dose, 8.7 mg) consistent with the observed response rate.

The observed response rates for this experiment were nonmonotonic, decreasing at some intermediate doses. This creates difficulty in reliable statistical estimation. Nonparametric methods of obtaining doses for ED<sub>x</sub> are available and could have been considered.<sup>2</sup> If a simple parametric model were desired, standard logistic regression analysis would have been preferred.

\* Available at: <http://www.r-project.org/>. Accessed April 7, 2004.

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*In Reply:*—We appreciate Dr. Pace's taking the trouble to examine our data on spinal bupivacaine for cesarian delivery.<sup>1</sup> Dr. Pace obtains results nearly identical to ours for successful operation but different results for successful induction, particularly the estimate of ED<sub>95</sub>. Dr. Pace graciously attributes these differences to our use of NONMEM (NONMEM Project Group, University of California, San Francisco, CA), and raises several important questions about using NONMEM for binary data.

Unfortunately, the explanation for the difference is more prosaic. On reexamining our analysis, we discovered an error in our data files analyzed by NONMEM. Dr. Pace correctly inferred our success/failure data from figure 1 of the article. We refit the data using both NONMEM and Excel (Microsoft, Redmond, WA), obtaining results identical to those of Dr. Pace (table 1).

Believing that the differences in results were related to the use of NONMEM, Dr. Pace raised four objections to our modeling approach. His objections raise several important considerations about logistic regression analysis to which we wish to respond.

First, Dr. Pace observes that the steepness parameter  $\gamma$  has no mechanistic interpretation. It simply describes the shape of the distribution.

Second, Dr. Pace points out that estimating interindividual variability with only a single observation in each individual is highly suspect. We agree, which is why we did not estimate interindividual variability in our analysis. As pointed out by Dr. Pace, this has already been addressed in *ANESTHESIOLOGY*. "Naive pooled data" is the correct description of the approach taken when data from multiple patients is fit while ignoring intersubject variability, as was done in this article.

Third, NONMEM and Rplus are performing identical calculations, and obtain nearly identical results. We also repeated the analysis with Excel, with assistance from Steven L. Shafer, M.D. (Professor, Anesthesiology Service, Palo Alto Veterans Affairs System, Palo Alto, California) and obtained identical estimates to those from NONMEM. We are puzzled at Dr. Pace's concerns about "extremely complex [calculations], involving many assumptions." The objective function for logistic regression is simply the calculation of a probability. The probability of multiple observations is the product of the probability of each individual observation, a readily computed number. Finding the parameters of the model that maximize probability of the observations with a naive pooled data approach requires virtually no assumptions at all, which is why a simple Excel spreadsheet and NONMEM generate identical results. We do observe, though, that it is not appropriate to use the Laplacian transformation when estimating single-subject data

(i.e., when using a naive pooled data approach). Although we reported in the manuscript that the Laplacian option was used, it had no effect because interindividual variability was not estimated.

Dr. Pace suggests fitting ED<sub>95</sub> rather than ED<sub>50</sub>. We agree and wish to elaborate on this observation. With a little algebra, one can express ED<sub>50</sub>, the dose associated with 50% probability of success, as a function of ED<sub>95</sub>, the dose associated with 95% probability of success. To be specific,  $ED_{50} = 0.0526326^{1/\lambda} ED_{95}$ . This can be readily substituted into the relation between dose and probability:

$$P = \frac{D^\lambda}{ED_{50}^\lambda + D^\lambda},$$

yielding the formula to estimate the ED<sub>95</sub> from the data, rather than estimate the ED<sub>50</sub> from the data,

$$P = \frac{D^\lambda}{(0.0526326^{1/\lambda} ED_{95})^\lambda + D^\lambda}.$$

More generally, if one wishes to estimate ED<sub>x</sub>, the effective dose associated with probability x, the formula is simply

$$P = \frac{D^\lambda}{\left(\left(\frac{1-x}{x}\right)^{1/\lambda} ED_x\right)^\lambda + D^\lambda}.$$

These formulas can be used in NONMEM, Excel, or any other estimation tool. The point estimates from such an estimation should be identical with those derived by calculating ED<sub>95</sub> from ED<sub>50</sub> and  $\gamma$ , but if the program can generate SEs, confidence intervals can be constructed from the SE estimates. This is the only real advantage of estimating ED<sub>95</sub> directly, but confidence bounds about the ED<sub>95</sub> estimate may be clinically important. Again, whether one uses NONMEM or another tool is irrelevant; all should return nearly identical answers, provided they maximize likelihood.

Fourth, we agree that the standard quantal sigmoid Emax model enforces a logarithmic dose transformation. Fortunately, drugs tend to work on a more or less logarithmic scale, and we think about drugs on a log scale (e.g., a typical clinical guideline is "the correct dose is half to twice the nominal dose," which reflects log spacing of dose). It is nonsensical to say "the standard model enforces X, Y, or Z" because, by definition, the standard is what it is. The users of the model are free to change it any way they desire, but of course, the changed model is then no longer the "standard" model. In this case, the user is free to substitute log dose, Exp(dose), or any desired transformation of dose into the "standard quantal sigmoid Emax" model if the user believes that is a better reflection of either the data or the underlying biology. Of course, the result is no longer the standard model but a nonstandard model, and the use of a nonstandard model would have to be justified based on pharmacology, biology, or goodness of fit to the data. However, that is only a modest hurdle for the modeler. Dr. Pace notes that the observations were evenly spaced doses, suggesting a logarithmic

**Table 1. Successful Anesthesia at Different Doses of Intrathecal Bupivacaine: ED<sub>50</sub> and ED<sub>95</sub> for Success<sub>induction</sub> and Success<sub>operation</sub>\***

	ED <sub>50</sub> ± SE	$\gamma$ ± SE	ED <sub>95</sub> ± SE
Success <sub>induction</sub>	6.50 ± 0.44	10.3 ± 2.8	8.65 ± 0.46
Success <sub>operation</sub>	7.64 ± 0.45	8.16 ± 2.1	11.0 ± 0.95

transformation seemed unnecessary. The spacing of the doses has little to do with the preferred model, because it is the response to the dose, not the spacing of the doses, that determines the shape of the curve.

We agree that, in general, if  $ED_{95}$  is of clinical interest, an  $ED_{95}$  calculated from all the data (*i.e.*, reestimating the model parameterized in terms of  $ED_{95}$  and  $\gamma$ ), rather than calculated from the  $ED_{50}$  and  $\gamma$ , is probably the optimal method of analysis. The point estimate will be the same, but the SEs will be estimated about the parameter of clinical interest. However, using NONMEM or any other estimation tool should give essentially identical results for this simple problem. The standard quantal sigmoid Emax model, mathematically modified as shown above, is perfectly appropriate to calculate  $ED_{95}$  or any other clinically relevant dosage.

Even though the results changed slightly with the corrected data analysis, the conclusion remains unchanged. The data strongly support

using doses of 11–12 mg bupivacaine for single-shot spinal anesthesia for cesarean delivery. The use of smaller doses increases the likelihood of inadequate neuraxial anesthesia.

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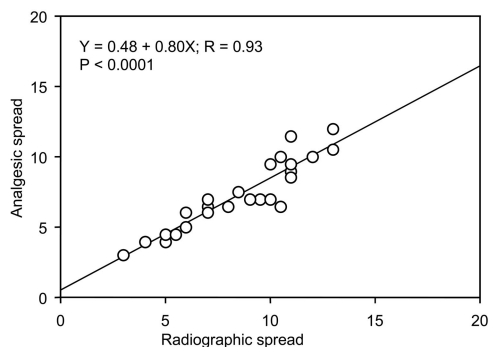
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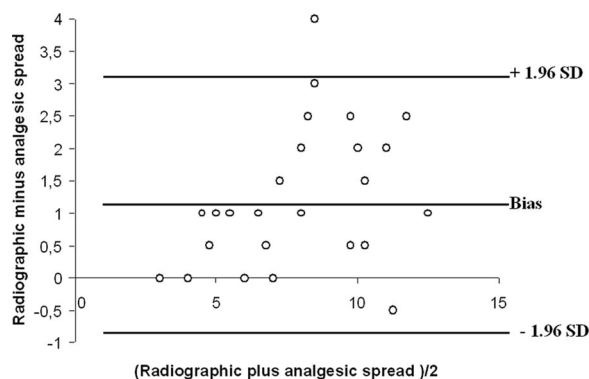
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## Can Epidurography Help to Predict the Extent of Epidural Blockade?

*To the Editor:*—We read the study from Yokoyama *et al.*<sup>1</sup> that sought to predict the extent of epidural blockade from the distribution of contrast medium injected into the epidural space. This study documents a linear correlation between radiographic and analgesic spread in 90 patients. The authors conclude that epidurography helps to predict the exact dermatomal distribution of analgesic block. Although



**Fig. 1. Correlation between radiographic and analgesic spread. From individual data reported in fig. 4<sup>1</sup>.**



**Fig. 2. Agreement between radiographic spread and analgesic spread using Bland and Altman plot. The mean bias was 1.12, with limits of agreement of  $-0.85$  and  $3.10$ . From individual data reported in fig. 4<sup>1</sup>.**

it is not surprising that the distribution of radiographic spread is well correlated with the spread of analgesic block, this does not mean that it is a reliable technique and that the two methods agree. The comparison could be better performed using the Bland and Altman method allowing determination of the bias and the accuracy of measurement.<sup>2</sup> We used individual data reported in Yokoyama *et al.*'s<sup>1</sup> figure 4 in the 16 patients who received 5-ml and 10-ml epidural injections to calculate the correlation (fig. 1) and also to assess the bias and limits of agreement (fig. 2). The correlation between the methods was confirmed ( $r = 0.93$ ,  $P < 0.001$ ; fig. 1) despite an inadequate agreement (bias = 1.1, SD = 1.0). If we consider the limits of agreement, it appears that from one patient to another, the difference between radiographic and analgesic spread may range from less than one segment to three segments. In these 16 patients, the mean radiographic spread was  $6.7 \pm 2.1$  segments after the 5-ml injections and  $9.4 \pm 2.7$  segments after the 10-ml injections. Consequently, the radiographic spread may overestimate the extension of epidural blockade, at most, of 44% and 32%, respectively. Moreover, the Bland and Altman plot shows that 1) when a difference exists between the two methods, the radiographic spread overestimates the analgesic spread in all cases except one and 2) the scatter of the difference seems to increase with the increase of analgesic and radiographic extension. The injection of a volume of local anesthetic or contrast medium greater than 5 ml or 10 ml, corresponding to the current clinical practice, may thus result in a greater discrepancy between the clinical and the radiographic evaluation of the block. Epidurography is therefore a useful tool to check the adequate position of the catheter but is less reliable to predict the extent of the block.

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**In Reply:**—We are grateful to Dr. Marret *et al.* for their constructive comments. We agree with their comment that “although the distribution of radiographic spread is well correlated with the spread of analgesic block, this does not mean that [epidurography] is a reliable technique and that the two methods agree.” We also do agree that the Bland and Altman method is proper to confirm whether the two different methods agree.

However, we have not shown the agreement of the two methods; we have rather shown the correlation. In our article, we confirmed that the distribution of radiographic spread correlates well with the spread of analgesic spread. Dr. Marret *et al.* have noted this correlation in their figure 1 ( $Y = 0.80 X + 0.48$ ;  $r = 0.93$ ,  $P < 0.0001$ ). This is what we intended to mention in our manuscript. We have not mentioned that the distribution of radiographic spread agrees with the spread of analgesia completely. Dr. Marret *et al.* point out that the radiographic spread overestimated the analgesic spread in all cases. However, we have neither overestimated nor underestimated those values. We have investigated the correlation between those values, and we got the

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relation expression; the analgesic spread =  $0.8 \times$  the radiographic spread. This means that, for example, if the radiographic spread is 10 segments, the analgesic spread would be approximately eight dermatomes in many cases.

We understand the comments regarding the bias and limits of agreement. However, we believe that this method is very useful to predict the dermatomal distribution of analgesic block because it is impossible to predict the cephalad and caudal spread of anesthetic, whether it will spread unilaterally and the general pattern of spread without epidurography. Thus, we concluded that epidurography could help to predict the dermatomal distribution of analgesic block.

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## Water versus Air Warmers

**To the Editor:**—Taguchi *et al.*<sup>1</sup> stress the essential role of skin temperature and Newton's Second Law of Thermodynamics in increasing core temperature ( $T_c$ ) with skin warming systems, but they do not demonstrate this role and they confuse other issues.

To increase  $T_c$  directly, the Second Law requires that the warming system's average cover temperature ( $T_{cwr}$ )  $>$  the mean skin temperature of multiple skin sites ( $T_{msk}$ )  $>$   $T_c$ . To demonstrate this, figure 1 shows that in 12 post aortocoronary bypass patients rewarmed for 2 h under a 1.8 m<sup>2</sup> radiant ceiling, the change in  $T_c$  ( $\Delta T_c$ ) occurred only

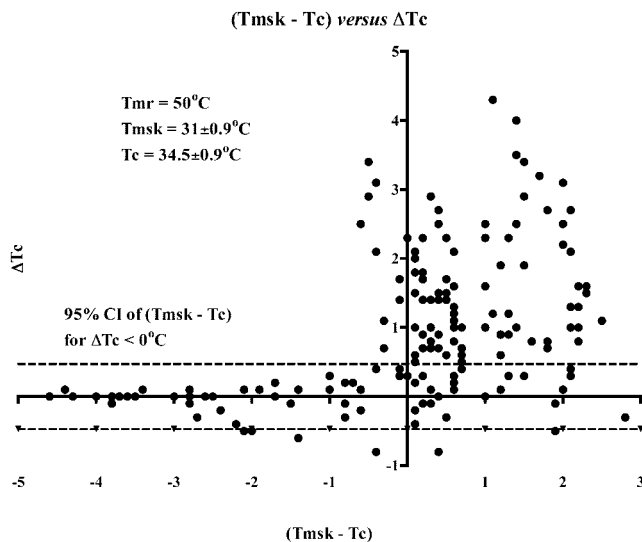
when ( $T_{msk} - T_c$ )  $>$  0°C. If the temperature gradient is  $T_{cwr} >$   $T_{msk} <$   $T_c$ , then heat passes from the cover to the skin but not to the core, and the warmer acts as an insulator, increasing  $T_c$  indirectly by retaining metabolic heat in the core.

Instead of  $T_{msk}$  the authors derive the peripheral temperature of the limbs ( $T_{perif}$ ). If  $T_{perif}$  represents the buffer between  $T_{cwr}$  and  $T_c$ , then  $T_c$  did not increase directly because  $T_{perif} <$   $T_c$ . Nor did  $T_c$  increase indirectly, for metabolic heat production was similar in both groups but  $\Delta T_c$  was not. What clinically relevant and measurable temperature gradient explains the increase in  $T_c$ ?

Heat content differences between periphery and core do not reflect tissue insulation. The units of insulation (*i.e.*, thermal resistance) are temperature gradient/heat transfer rate (°C/kCal/h or °C/W), not heat content (kCal or kJ). Tissue insulation is proportional to the temperature gradient required to cause heat transfer and increase  $T_c$ , which, in fig. 1, required a ( $T_{msk} - T_c$ ) of  $1 \pm 0.8^\circ\text{C}$  ( $n = 94$ ). In the authors' study  $T_{perif}$  represented a heat sink and heat transfer to the core was “constrained” by the lack of an appropriate temperature gradient rather than by tissue insulation.

Peripheral heat content increased 2.1–2.5 times more than core because initially  $T_{perif} <$   $T_c$  (water,  $-2.6^\circ\text{C}$ ; air,  $-2.1^\circ\text{C}$ ) and, therefore, exposed to the same  $T_{cwr}$ , the periphery warmed preferentially. Calculated from the change in heat content at the end of warming ( $\Delta Q$ , their fig. 4),  $\Delta T_c = +2.9^\circ\text{C}$  (water) and  $+1.7^\circ\text{C}$  (air), as shown in their figure 3. Similarly,  $\Delta T_{perif} = +5.8^\circ\text{C}$  (water) and  $+4^\circ\text{C}$  (air). Therefore, their data implies a final ( $T_{perif} - T_c$ ) of  $+0.3^\circ\text{C}$  (water) and  $+0.2^\circ\text{C}$  (air), which is more consistent with the Second Law and the observed increase in  $T_c$  than the “ $-0.8^\circ\text{C}$ ” shown in their figure 5.

At the end of warming the change in heat content per unit area warmed was 1.25 times larger for water (185 kCal/m<sup>2</sup>) than for air (148 kCal/m<sup>2</sup>). Yet the authors write “. . . heat transfer (rate) per unit anterior area” was similar. This inconsistency results from the measurement method. Heat content is derived from temperature. Heat transfer rate per unit area, or “heat flux” ( $q$ ), is directly measured by heat flux transducers. Heat flux,  $q = \Delta T \cdot b$ , where  $\Delta T$  is the cover to skin temperature gradient across the heat flux transducers and  $b$ , from Newton's Law of Cooling, is the heat transfer coefficient (*i.e.*, the efficiency) of that particular system, usually expressed in W/m<sup>2</sup>·°C. For one conventional water mattress<sup>2</sup> (and three others, including a suit



**Fig. 1.** Twelve post aortocoronary bypass patients rewarmed for 2 h under a 1.8 m<sup>2</sup> radiant ceiling. X-axis: mean skin – tympanic core temperature ( $T_{msk} - T_c$ ) at 10-min intervals. Y-axis: the change in  $T_c$  from initial value ( $\Delta T_c$ ). The 95% confidence interval (CI) is for all values of ( $T_{msk} - T_c$ ) when  $\Delta T_c <$  0°C. The mean radiant temperature ( $T_{mr}$ ) at the patient (*i.e.*, the driving temperature for radiant heat exchange) and the initial values of  $T_{msk}$  and  $T_c$  are shown.  $T_{msk}$  was averaged from 4 skin sites: chest, lateral upper arm, thigh and lateral calf.

similar to this study)  $b$  was 1.5 times larger than that for four air warmers:<sup>3</sup>  $40 \text{ W/m}^2\cdot^\circ\text{C}$  versus  $26 \text{ W/m}^2\cdot^\circ\text{C}$ . The larger  $b$  of water means that the same  $q''$  will produce a smaller  $\Delta T$  than with air and, therefore, at the same  $T_{\text{cvr}}$ ,  $T_{\text{msk}}$  will be higher with water than with air—and heat content is derived from  $T_{\text{msk}}$ . Although  $T_{\text{cvr}}$  was not measured,  $T_{\text{msk}}$  was, and it would be instructive to know the  $T_{\text{msk}}$  difference between the systems.

The change in heat content/warmed area for water was 1.25 times that of air, not 1.5 times, as the ratio of their  $b$  values suggests, because  $\Delta T$  differed. The air warmer was set to “ $43^\circ\text{C}$ .” The low heat capacity of air and environmental heat loss would degrade  $T_{\text{cvr}}$  to a relatively constant  $T_{\text{cvr}} < 43^\circ\text{C}$ . The water system was set to a target  $T_c$  of “ $37^\circ\text{C}$ .” The high heat capacity and mass flow rate of water would prevent  $T_{\text{cvr}}$  environmental degradation. But the system’s servocontrol algorithms would produce a variable  $T_{\text{cvr}}$ : initially high ( $40^\circ\text{C}$ ) but decreasing as  $T_c$  increased. As  $T_{\text{cvr}}$  decreased,  $(T_{\text{cvr}} - T_{\text{msk}})$  also decreased until, finally, the water heat transfer rate equaled that of air (their fig. 1). Had  $\Delta T$  been the same, the difference between the systems would have been greater.

It is improbable that an air warmer above the body and water mattress below would match the heat transfer of a water suit because above the body, the change in heat content/warmed area was less with air than with water and below the body, a contour-conforming water suit gives better skin contact, which is essential for conductive heat transfer, than a flat mattress.

This was a sophisticated study of thermoregulatory physiology rather than heat transfer physics. It did not report those fundamental differences in the heat transfer characteristics (*i.e.*,  $T_{\text{cvr}}$ ,  $T_{\text{msk}}$ , and  $b$ ) that must be known to safely and effectively exploit the full potential of any skin-warming system. The heat transfer rate, in isolation, is a description of what happened in a specific application. It is not an

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*In Reply:*—It is well established that peripheral tissues act as insulators and that the efficacy of this insulation is a strong function of vasomotor status.<sup>1</sup> For example, surface warming is more effective when humans are vasodilated because vasodilation allows facile flow of heat from the skin surface through peripheral tissues to the core.<sup>2</sup> Our article again illustrates the importance of thermal insulation provided by peripheral tissues in that the increase in peripheral tissue heat content was many-fold greater than the increase in core heat content during the first hour of warming.

Peripheral tissue temperature was lower than core temperature throughout the study, which precludes direct warming of the core. However, peripheral tissue temperature was consistently greater during circulating-water warming than during forced-air warming. Therefore, less heat left the core with circulating-water warming and core temperature increased approximately 30% faster. Consistent with faster rewarming, our figure 5 shows that the core-to-peripheral tissue temperature gradient was slightly less with circulating water. In both cases, core warming resulted from the combination of metabolic heat production and the insulating effects of warmed peripheral tissues. Such indirect core warming is a well-established phenomenon<sup>3</sup> and is probably the mechanism by which nearly all clinical warming systems augment core temperature.

We do not understand how Dr. English estimates the core-to-peripheral tissue temperature gradient from core temperature and the change in peripheral tissue temperature without knowing the initial peripheral tissue temperature. Our figure 5 is correct and shows that peripheral tissue temperatures were roughly  $0.8^\circ\text{C}$  less than core temperature throughout warming.

Dr. English’s assertion that “above the body, the change in heat content/warmed area was less with air than with water” is curious because it is impossible to attribute observed changes in peripheral tissue heat content to anterior *versus* posterior warming. Heat transfer rates should therefore be measured with thermal flux transducers

rather than estimated from tissue heat content. Despite Dr. English’s assertion to the contrary, this is exactly what we report; anterior heat flux was identical with each tested warmer.<sup>4</sup>

Dr. English has reported results in terms of  $b$ , which is the heat flux divided by the warmer-to-skin temperature difference. As illustrated by his own example, this is a suboptimal measure because the tissue-temperature difference is a function of the heater and tissue characteristics and therefore varies markedly over time. Actual heat transfer rates, the clinically relevant measures of heater efficacy, differ less than might be expected based on  $b$ .

We are mystified by Dr. English’s assertion that “the change in heat content/warmed area for water was 1.25 times that of air, not 1.5 times, as the ratio of their  $b$  values suggests.” We did not report  $b$  or the results that would be necessary to calculate this value. Unlike forced-air warming, the circulating-water system we tested includes a servocontrol algorithm. Because the system was set to  $37^\circ\text{C}$ , heating intensity presumably decreased as core temperature approached  $37^\circ\text{C}$ . Initial rewarming rates are thus a better indicator of system capability than rewarming rates near normothermia.

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We appreciate Dr. English’s assessment that our investigation<sup>4</sup> “was a sophisticated study of thermoregulatory physiology.” We note, however, that our volunteers were kept anesthetized throughout the protocol specifically to minimize thermoregulatory responses and allow us to isolate heat transfer characteristics that must be known to safely and effectively exploit the full potential of skin-warming systems. Specifically, we evaluated and reported cutaneous heat transfer, regional body heat content, and core rewarming rates—the clinically relevant system characteristics.

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Anesthesiology 2005; 102:481

## Propofol and Sleep: An Attractive Connection

*To the Editor:*—My 25-yr personal experience considering the choice of drugs for self-administration by physicians, excepting the standbys alcohol, opioids, and stimulants, has usually generated fairly predictable questions. One common query is “why in the world would anyone abuse that” at some time during the evaluation. In fact, the first published report<sup>1</sup> of propofol abuse more than 10 yr ago generated exactly this question. Often, even after time in an established recovery, a satisfactory response to this query is not forthcoming.

The recent paper by Tung *et al.*<sup>2</sup> may represent a unique clear insight into the reinforcing properties of propofol self-administration that helps answer the “why in the world” question, at least for this drug. Chronic fatigue from repetitive extended workdays and longer evenings/nights is an inescapable part of a busy practice. Sleep deprivation resulting from inadequate duration or poor quality of sleep represents a major impetus for research into pharmacologic sleep augmentation for those living with recurring daytime exhaustion.

The editorial<sup>3</sup> accompanying the paper by Tung *et al.* proposed that perhaps someday patients might emerge from prolonged sedation feeling refreshed and rested. Might I suggest that there are some

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The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required.—Michael M. Todd, Editor-in-Chief.

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## Use of the Laryngeal Tube-S™ for Airway Management and Prevention of Aspiration after a Failed Tracheal Intubation in a Parturient

THE laryngeal tube-S™ (LTS™; VBM Medizintechnik, Sulz, Germany) is a new supraglottic airway-management device introduced into the European market in 2002 (fig. 1). It is a newer generation of laryngeal tube which is fitted with a second lumen serving for suctioning, and free gastric drainage. This case report describes the use of the LTS™ for emergency airway management of a parturient after failed attempted tracheal intubation.

A 27-yr-old parturient was brought to the operating theatre for urgent Cesarean section due to prolonged rupture of the amniotic membrane. Her medical history was unremarkable. She had eaten nothing for about 12 h and didn't have any symptoms of gastroesophageal reflux. Upper-airway examination revealed score II of Mallampati,<sup>1</sup> an interincisor gap of about 4 cm, and a thyromental distance of about 2.5 finger breadths. She had limited (less than 30°) extension of the neck. General anesthesia was chosen due to the patient's refusal

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historical hints in the form of case, and sometimes coroner, reports, that uncontrolled research on this subject has been underway for more than a decade? If indeed propofol immediately induces sleep that mimics the best properties of non-drug-assisted rest, including deprivation recovery, then the attraction can become, for a few, overwhelming, despite constant personal danger. For someone with a long-standing concern with physician well being and chemical dependency, the response to the titles alone, of the paper and editorial, prompted the response “so that's it.”

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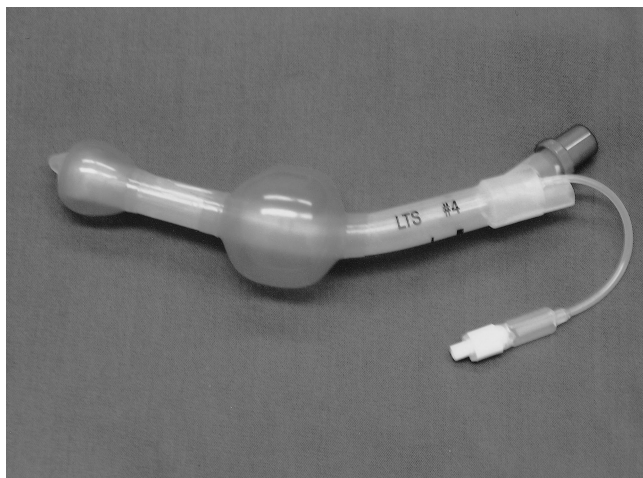
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of regional anesthesia. After preoxygenation, the patient was anesthetized with a rapid sequence induction: using 450 mg of sodium thiopental and 120 mg of succinylcholine. The Sellick maneuver was applied as recommended by an assistant. A grade III view of the larynx was obtained using a size-3 blade McIntosh laryngoscope. Two attempts at intubation, at the optimal sniffing position by the clinical-anesthesia 3-year resident, without and with a stylet, failed. Release of cricoid pressure didn't improve the view, and the pressure was applied again. A senior anesthetist was called. The oxygen saturation decreased to less than 50%. Two-person manual bag and mask ventilation with 100% oxygen was difficult and resulted in only a modest increase in oxygen saturation (60-70%). A size-4 LTS™ was blindly inserted about 5 min after induction, and its cuff inflated with about 80 ml of air. The patient could be ventilated easily and the oxygen saturation increased to 97% using manual ventilation with 100% oxygen. The patient regained consciousness and as she started breathing she began to move her eyelids. Regurgitation of yellowish stomach contents began with the LTS™ in place but it was drained by the suctioning lumen of the LTS™ and no change in oxygen saturation was detected. A nasogastric tube was inserted and about 30 ml of fluid drained from the stomach.





**Fig. 1.** The laryngeal tube-S™ (LTS™; VBM Medizintechnik, Sulz, Germany).

At this time the patient was alert and cooperative. She was reassured and the LTS™ was removed in the presence of the consultant anesthesiologist. Examination of its cuff showed no blood traces. The obstetrician was asked if it was possible to administer regional anesthesia and she agreed after she assessed the fetal heart sound with a sonicaid. Afterwards, there was no evidence of aspiration at any stage of the procedure. Spinal anesthesia was administered and a healthy girl was delivered (weight, 3900 g; APGAR scores 9 and 10 after 1 and 5 min, respectively). A full explanation of the events was given to the patient and her husband. The patient and her baby were discharged from the hospital in good condition 2 and 4 days later, respectively.

## Discussion

Difficult or failed tracheal intubation is an important cause of anesthetic-related maternal morbidity and mortality.<sup>2</sup> Regurgitation is a rare but significant cause of morbidity and mortality after failed tracheal intubation.<sup>3</sup>

Considering our management the following should be noted.

1. Omission of antacid premedication was an error.
2. The selected dose of succinylcholine was relatively high.<sup>4</sup>
3. Release of the Sellick maneuver after failed intubation and difficult ventilation are controversial and not routinely recommended.<sup>5</sup>
4. It was quite possible that the patient could have been intubated successfully, if another size or type of laryngoscope blade had been used. However, these issues are not the focus of this case report.

Although the *Laryngeal Mask Airway*™ (LMA™; Laryngeal Mask Company Limited, San Diego, CA) has been successfully used and promoted for management of failed obstetric intubations<sup>6-8</sup> it is not effective in all patients.<sup>9</sup> The LMA™ may yield in unsuccessful ventilation and gastric inflation due to low median airway-seal pressure and it does not reliably protect against aspiration of regurgitated stomach contents.<sup>10</sup> A recent case

report regarding the use of the *ProSeal*™ laryngeal mask airway (PLMA™; Laryngeal Mask Company Limited) for emergency airway management after failed tracheal intubation during Cesarean section has been published.<sup>11</sup> Also there are a few reports describing prevention of aspiration of gastric contents with the PLMA™ *in situ*.<sup>12-15</sup> These reports suggest the effectiveness of the PLMA™ to maintain the airway and prevent aspiration in elective and emergency situations. However, in our case a PLMA™ was not ready to use.

The LTS™ may be a good choice for emergency airway management.<sup>16-18</sup> It may provide a higher airway seal than the LMA™: an airway pressure as high as 40 cm of H<sub>2</sub>O would be achievable without gastric inflation and its insertion time is also comparable with that of the LMA™.<sup>19,20</sup> Appropriate positioning of the LTS™ has been verified with fiberoptic endoscopy in all patients.<sup>20</sup>

In contrast to the combitube, the LTS™ has only one adapter that may be connected with a ventilation device, whereas the remaining connector can only be connected to a suction adapter. This may provide additional patient safety in order to prevent an inexperienced user inadvertently attaching the Y-piece to the esophageal tubing.

The LTS™ has encountered some minor problems, so that some may consider it a suboptimal device. Firstly, there are few controlled trials comparing the LTS™ with other similar supraglottic devices such as the PLMA™, LMA™, and combitube. Secondly, it has never been tested in hypoxic and/or hypercarbic patients, as in our presented case. Thirdly, there may be concerns, although unlikely, that the LTS™ may induce dangerous effects like the esophageal obturator. Fourthly, there may be dangerously high cuff pressures when the device is used in an emergency situation to secure the patient's airway. This is not a major problem, since the cuff pressure of the LTS™ (80 cm of H<sub>2</sub>O) has been reported to be much lower than that of the combitube (80–300 cm of H<sub>2</sub>O) and the LMA™ (100–250 cm of H<sub>2</sub>O).<sup>20,21</sup>

In conclusion, in the future, the LTS™ may have a role in emergency obstetric airway management.

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## Transesophageal Diaphragmatic Pacing for Treatment of Persistent Hiccups

*To the Editor:*—Almost everyone has had the hiccups at one time or another. These involuntary contractions of the diaphragm and respiratory muscles that terminate with abrupt closure of the glottis—or “hiccups”—are usually transient and do not herald any serious pathology. Occasionally, hiccups persist, lasting hours, days, or weeks. Hiccups lasting longer than 48 h are termed “persistent” and those lasting longer than a month are termed “intractable.” Persistent or intractable hiccups may be the presenting symptom of serious pathology.

Despite the varied possible etiologies, in the majority of cases no organic causes can be identified and a diagnosis of idiopathic chronic hiccups is made. As expansive as the potential causes is the list of potential cures. Home remedies such as breath holding, a glass of water, and even a scare to evoke a startle reflex have been tried. Pharmacologic interventions are just as varied. Indeed, several agents used to cure hiccups (i.e., midazolam and dexamethasone) have anecdotally been suspected as causative agents. Having exhausted pharmacologic remedies, some have tried more invasive techniques such as acupuncture, glossopharyngeal nerve block, phrenic nerve block, and even general anesthesia.

We treated one patient with the use of the transesophageal atrial pacing probe to alleviate his persistent hiccups after revision of a right hip prosthesis.

The patient was a 76-yr-old man with a history of osteoarthritis and right total hip arthroplasty, who returned to the operating room for revision of a painful loose acetabular implant. Preoperatively, the patient had a lumbar epidural catheter placed in the holding area. He was given midazolam 2 mg intravenously for sedation without complication. He underwent revision of the right hip prosthesis under general anesthesia without incident. The epidural was bolused with bupivacaine 0.25% before emergence. The patient was extubated in the operating room and transported to recovery, where a continuous infusion of 0.0625% bupivacaine and fentanyl 10 µg/ml at a rate of 3.5 ml/h was started. On rounds the next morning, the patient complained of hiccups that had started the evening before and persisted through the night. He denied any other symptoms and rated his pain control as good. Physical exam was unremarkable except for persistent hiccups. Initial pharmacologic interventions included Thorazine 10 mg, twice, Dilantin 200 mg, and lidocaine 100 mg intravenously; all failed to resolve the hiccups. Next, topical lidocaine spray applied to the oro-

pharynx was tried without relief. Finally, after topical anesthesia with Cetacaine spray was achieved, the patient swallowed the 18-French transesophageal atrial pacing probe (Tapscope model 550F; CardioCommand, Tampa, FL). The probe was connected to the pulse generator (Tapsystem model 2A; CardioCommand) and the diaphragm was paced at a rate of 80 bpm with 20 mA output for 15 s. The generator was then turned off and the patient's hiccups had resolved. The hiccups did not reoccur for the remainder of his hospitalization.

Our patient had reported persistent hiccups after his original total hip arthroplasty. The hiccups had lasted for more than 1 week. The patient had tried mints, which helped but did not resolve the hiccups. For both procedures, our patient had had an epidural placed for postoperative pain control. In addition, our patient had received midazolam for sedation during epidural placement, another possible cause for the hiccups. However, no other organic cause for the hiccups was identified.

Gastroenterologists have advocated cisapride, omeprazole, and baclofen as the initial treatment for patients with persistent hiccups. However, the results of transesophageal atrial pacing probe pacing the diaphragm produced rapid and complete relief. Treatment parameters of frequency and duration were estimates based on clinical experience and patient comfort. Amplitude and probe position was assessed objectively by successful diaphragmatic pacing as determined by changes in respiratory pattern.

It should be noted, however, that the transesophageal atrial pacing probe is not an entirely benign intervention. Future applications of transesophageal atrial pacing probe placement for diaphragmatic pacing should include standard monitors (blood pressure, electrocardiogram, and pulse oximetry) to insure patient safety. In our case, the transesophageal atrial pacing probe for the resolution of persistent hiccups worked; however, a randomized prospective study is warranted to more fully evaluate the efficacy and safety of this treatment modality.

Special thanks to Jolene Bean-Lijewski, M.D., Ph.D., Associate Professor of Anesthesiology, and Jeff R. Gibson, Jr., M.D., Assistant Professor of Anesthesiology, Scott and White Memorial Hospital, Texas A&M University College of Medicine, Temple, Texas, for their editorial talents in reviewing this letter.

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## A Simple and Effective Technique to Increase Oxygenation for Patients with Nasal Cannulae during Upper Endoscopy

*To the Editor:*—Moderate intravenous sedation is routinely administered for diagnostic and interventional procedures to alleviate patient discomfort and anxiety. Oxygen desaturation is a common problem for anesthesiologists providing moderate sedation to patients undergoing upper endoscopy (esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, or bronchoscopy). During these procedures, patients typically receive intravenous propofol for sedation while supplemental oxygen is administered *via* nasal cannulae. The nasal cannula often becomes an ineffective tool for providing supplemental oxygen when the patient's mouth is open and the endoscopy probe is in place. We would like to report a technique that is simple and effective for increasing oxygenation in patients receiving moderate intravenous sedation as described above.

After the patient assumes the lateral decubitus or prone position, we place a clear plastic sheet over the patient's face and tape it to the patient's head (fig. 1). The nasal cannula is thus effectively converted into a face tent. This technique creates an oxygen reservoir that provides an inspiratory fraction of oxygen of 40–60% with oxygen flows of 4 l/min. After preoxygenation using this technique for a few minutes, we usually titrate intravenous propofol to achieve moderate-to-deep sedation while maintaining spontaneous respiration without oxygen desaturation. We monitor the patient's respirations with capnography or a pediatric precordial stethoscope placed over the trachea. If the patient becomes apneic because of airway obstruction or oversedation, we still have an average of 2 to 3 min to manipulate the airway before oxygen desaturation occurs.

We make a 12" × 12" or larger plastic sheet using any clean, clear plastic bag (nasal cannula bags, specimen bags, or breathing circuit bags) or the plastic cover from the upper body warming blanket kit. After explaining to the patient that by applying this plastic sheet we will be increasing their oxygen supply, even the most anxious patients are receptive. One concern is that a plastic sheet could increase "dead space" resulting in rebreathing of carbon dioxide and hypercarbia. We routinely monitor rebreathing of carbon dioxide using capnography for prolonged cases or whenever it is available. By maintaining the plastic sheet in a tent-like position covering only the upper two thirds of the head or using oxygen flow greater than 4 l/min, we can avoid



**Fig. 1. A simple and effective technique to increase oxygenation for patients with nasal cannulae during upper endoscopy. Placing a clear plastic sheet covering the head converts a nasal cannula to a face tent. This face tent increases oxygen reservoir for upper endoscopic procedures in the lateral decubitus position.**

rebreathing of carbon dioxide and hypercarbia. There is minimal (0–3 mmHg) carbon dioxide rebreathing with this face tent. During manipulation of the endoscopy probe, we lift the plastic sheet slightly to avoid dragging it into the mouth.

Although there are commercially available masks for bronchoscopy, this technique uses plastic sheets that are ubiquitous and available at no additional cost. We also use this technique for patients undergoing colonoscopy in the lateral decubitus position, rectal procedures in the jackknife position or pain management procedures in the prone position.

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