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Effect of alkalinized mepivacaine for epidural anesthesia on the skin temperature and skin blood flow: A mathematical analysis by simulation model

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Abstract: The changes in skin blood flow after barbiturate injection are predictable based upon changes in skin temperature, assuming that these changes are followed by ramp function of the first-order system composed of blood vessel-tissue-skin. We applied this simulation model to epidural anesthesia, and investigated the analogy between theoretical and measured values using 2% alkalinized and nonalkalinized mepivacaine. During epidural anesthesia, a Laser Doppler flowmeter and a skin temperature probe were used to simultaneously measure skin blood flow and skin temperature. The onset time of increases in skin temperature and blood flow in the alkalinized group was shortened by one-fourth of that of the nonalkalinized group. In the nonalkalinized group, the pattern of changes in skin blood flow could not be predicted using the mathematical model. In the alkalinized group, however, the skin blood flow change was in accord with the theoretical values calculated from the skin temperature. These results indicate that the precise prediction of measured values by the simulation model is dependent on the speed of the sympathetic blockade. Conversely, the response to sympathetic nerve and blood vessels in different conditions can be assessed using this simulation model.

Key words: Epidural anesthesia—Alkalinized mepivacaine—Skin blood flow—Skin temperature—Laser Doppler—Mathematical model

Introduction

There are many transient phenomena in biological systems such as the uptake and distribution of anesthetic gases and the bolus injection of drugs into the vein. The response of biological systems to stimuli is not always the same. Previously, we demonstrated that the changes in peripheral skin blood flow and skin temperature after barbiturate injection corresponded favorably with the simulation model when the temperature is considered as an output of the blood flow change in a basic first-order system composed of the blood vessel, tissue, and skin [1,2].

In the case of epidural anesthesia, vasodilatation occurs by the blockade of the sympathetic nerves, which in turn increases the skin blood flow and skin temperature. Therefore, this simulation model can be applied for epidural anesthesia to assess sympathetic blockade. The present study evaluates the usefulness of the simulation model in patients under different sympathetic blockades. In recent years, it has been reported that the onset of epidural anesthesia can be accelerated by elevation of pH in local anesthetics [3–5]. We therefore compared the concurrence of the simulation model to the actual changes in skin blood flow and temperature between alkalinized and nonalkalinized local anesthetics.

Patients and methods

After obtaining informed consent and Ethics Committee approval, we studied 50 patients (ASA I) undergoing lower abdominal surgery in the Department of Obstetrics and Gynecology in our hospital. Patients were randomly divided into two groups. All patients were premedicated with diazepam (10 mg, i.m.) and atropine (0.5 mg, i.m.) approximately 60 min before surgery. The temperature and humidity of the operating room were regulated at approximately 25°C and 60% in advance, respectively. After admission to the operating room, the probe for measurement of the skin temperature (Terumo, Tokyo, Japan.) was attached to the ventral side of the left big toe, and skin temperature was continuously recorded. The probe of the Laser Doppler flowmeter (ALF-2100, Advance, Tokyo, Japan) was attached 5 mm proximal to the temperature probe. Group I patients ($n = 25$) received 15 ml of plain 2%

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mepivacaine, and group II patients (n = 25) received 15 ml of alkalinized 2% mepivacaine. The alkalinized solution was prepared in the following manner: 2 ml of 7% $NaHCO_3$ was added to 20 ml of 2% mepivacaine, resulting in a final solution of pH 7.025 ± 0.017.

The patient was positioned in the lateral decubitus position. The epidural space was identified at L2-3 or L3-4 by loss of resistance to saline using a Tuohy needle. After puncture of the enpidural space, a 3-ml test dose of the local anesthetic solution was injected and an additional 12 ml (total 15 ml) was incrementally injected. The skin blood flow and skin temperature were continuously recorded during the procedures, and continued until these parameters reached equilibrium.

Theory

The change in skin temperature is assumed to be linearly proportional to the change in skin blood flow. Therefore, the change in skin temperature ($\Delta\theta$) is approximately proportional to the change in skin blood flow (ΔQ):

$$\Delta Q = C \cdot \Delta\theta \tag{1}$$

where c is the specific heat of the tissue.

If a biological system such as skin, tissue, and blood vessels is considered as a basic first-order system, then the change in skin blood flow (input) and skin temperature (output) is represented by this basic first-order system. It is reasonable to consider that an ideal step input cannot occur physiologically. In many biological systems, the input smoothly increases to time τ as shown in Fig. 1 (ramp function) [1,2].

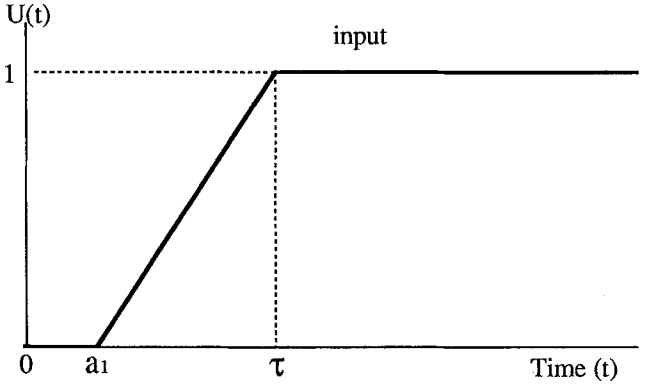

Fig. 1. Nonlinear input function modified from ramp function as a simulation of the change of skin blood flow. When local anesthetic is injected into the epidural space, initial blood flow (F_o) starts to elevate after a certain time lag (a_1) Thereafter, blood flow increases subsequently as a transient phenomenon until time tau (τ) when the blood flow reaches equilibrium

In equations such as $u(t) = 1/\tau\ (0 < t \leq \tau)$ and $u(t) = a\ (t > \tau)$, a transient and nonlinear input pattern as shown in Fig. 1 is considered as a simulation model for change in the skin blood flow:

$$u(t) = \begin{cases} \dfrac{t}{\tau}\ (0 < t \leq \tau) \\ 1\ (\tau < t) \end{cases} \tag{2}$$

In the s-domain using Laplace transformations, the function of the model is written as:

$$U(s) = \frac{1}{\tau s^2}(1 - e^{-\tau s}) \tag{3}$$

Then, the transfer function G(s) is:

$$G(s) = \frac{Y(s)}{U(s)} = \frac{Y(s)}{\dfrac{1}{\tau s^2}(1 - e^{-\tau s})} \tag{4}$$

Because G(s) is assumed to be $\dfrac{1}{1 + Ts}$ in this system, the output Y(s) is written as:

$$Y(s) = U(s) \cdot G(s) = \frac{1}{1 + Ts} \cdot \frac{1}{\tau s^2}(1 - e^{-\tau s}) \tag{5}$$

By solving Eq. (5) for t-domain using the inverse Laplace transformation, the following formula is obtained:

$$Y(t) = \begin{cases} \dfrac{t - T}{\tau} + \dfrac{T}{\tau} \cdot e^{-t/T}\ (0 < t \leq \tau) \\ 1 + \dfrac{T}{\tau}(1 - e^{-\tau/T}) \cdot e^{-t/T}\ (t > \tau) \end{cases} \tag{6}$$

where T is the time constant (see appendix).

The curve shown by eq. (6) is serial and smooth at $t = \tau$, and this curve has an inflection at $t = \tau$ because the second grade differential equation of Y(t) is positive at $t < \tau$, and negative at $t > \tau$.

The changes in skin blood flow and temperature experimentally obtained during epidural anesthesia are plotted in Fig. 2. The times required for skin blood flow and skin temperature increase after total epidural injection of local anesthetics were defined as a_1 (s) and b (s), respectively. After obtaining the point of maximum inclination on the curve of skin blood flow (derivative of the curve = 0), the following points were defined:

a_2 (s): time after administration of local anesthetics from the crossing points of the maximum inclination line and base line.

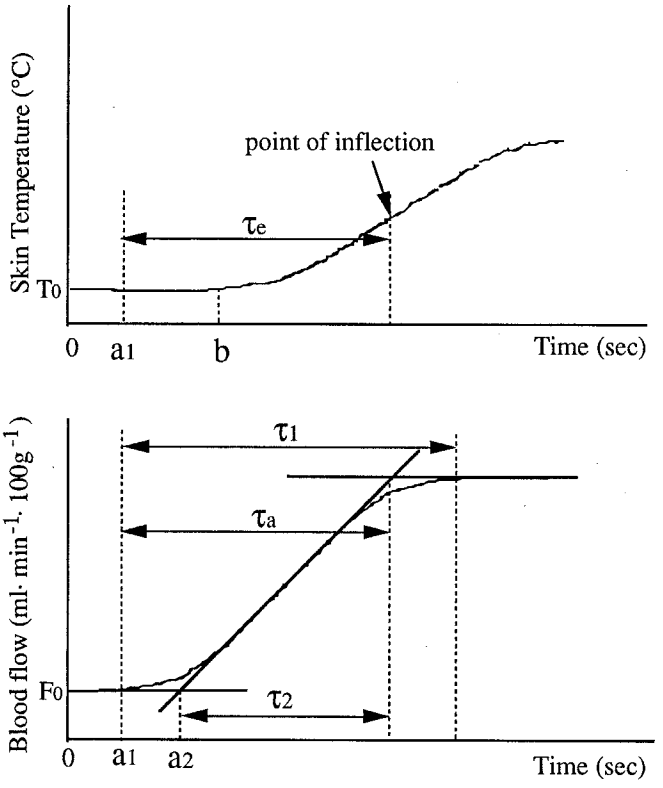

Fig. 2. Schema showing the recorded skin blood flow and skin temperature. The time which the skin blood flow and skin temperature start to increase are defined as t = a_1 and t = b, respectively. The time from a_1 to the time at which the blood flow plateaus is defined as tau 1 (τ_1). *Arrow* indicates the point of inflection. a_2, τ_1, and τ_2 are defined in the figure

τ_1 (s): time from a_1 to the point at which the skin blood flow reached a plateau.

τ_2 (s): time from a_2 to the point at which the above-mentioned inclination crossed the plateau line of the skin blood flow;

These values are obtained on the curve for each patient.

On the other hand, adverse changes in the skin temperature (ΔTS°C) were obtained by temperature probe, with τ (inflection point) of the curve, expressing the most compatible values with the experimental values which were recorded every 20 s.

Then, τ was calculated by a computer to make the sum of the squares of X(t) and Y(t) as small as possible.

Table 1. Patient characteristics

	Group I nonalkalinized (n = 25)	Group II alkalinized (n = 25)
Weight (kg)	54 ± 10	56 ± 10
Height (cm)	155 ± 5	154 ± 4
Age (years)	36 ± 11	39 ± 9

Values are mean ± SD. There are no significant differences between groups.

"The theoretical values of τ" and "τ obtained on the trace of skin temperature change" were defined as the estimated value (τ_e) and actual value (τ_a), respectively. τ_e and τ_a were compared in both groups.

All data are shown as mean ± SD. Analysis of variance was used for data comparison and $P < 0.05$ was considered statistically significant.

Results

Table 1 indicates that the two groups were similar in weight, height, and age. A summary of the data obtained from the changes in skin blood flow and skin temperature is shown in Table 2. Baseline skin blood flow (F_0) and skin temperature (T_0) did not differ in group I and group II patients. After administration of the total dose of local anesthetics, significant elevation of skin blood flow occurred in group II earlier than group I (a_1: 56 ± 64 *vs* 331 ± 165 s). The time at which skin blood flow reached a plateau after elevation (τ_2) was significantly shorter in group II than group I (140 ± 46 *vs* 209 ± 97 s).

The time required for increases in skin temperature after administration of the total dose of local anesthetics was significantly shorter in group II than in group I (b: 122 ± 86 *vs* 424 ± 167 s). The time required for skin temperature to plateau was significantly shorter in group II than in group I (419 ± 128 *vs* 711 ± 177 s).

The optimum estimated value (τ_e) obtained from the change in skin temperature was 171 ± 71 s in group I and 152 ± 77 s in group II. The actual value τ_a obtained from the trace of the changes of skin blood flow in each case was 240 ± 109 s in group I and 151 ± 45 s in group II ($P < 0.01$). The distribution of [τ_a–τ_e] in group II was close to zero and significantly less than group I (Fig. 3).

In both groups, no significant correlation was observed between the parameters obtained from skin blood flow change and body weight, height, and age. Furthermore there was no significant correlation be-

Table 2. Summary of data obtained from patients

	Group I (n = 25) nonalkalinized	Group II (n = 25) alkalinized
F_0	2.3 ± 0.7	3.0 ± 2.7
T_0	27.3 ± 1.7	29.4 ± 2.2
a_1	331 ± 165	56 ± 64*
b	424 ± 33	122 ± 17*
τ_1	347 ± 104	166 ± 53*
τ_2	209 ± 97	140 ± 46*
τ_a	240 ± 109	151 ± 45*
τ_e	171 ± 71	152 ± 78

Values are expressed as mean ± SD.
* P , 0.05 *vs* group I. $\tau a = \tau 2 + (a_2 - a_1)$

tween the parameters obtained from skin temperature change and body weight, height, and age.

Discussion

It is generally considered that the effect of blood flow on skin temperature is influenced by ambient temperature and the temperature of the dermis [6]. Assuming that the dermal temperature is constant and there is no sweating, skin temperature variation is dependent upon the thermal conduction of the skin [7]. In addition, the effect of laser Doppler flowmetry on skin temperature was judged to be minimal because flowmetry radiates within the hemispherical region of approximately 1 mm from the tip of the probe. Under these conditions, it has been reported that neither the radiation nor conduction of heat energy participates in the accommodation of heat exchange of the skin because these are negligible in comparison with the heat exchange due to blood flow [6]. Indeed, changes in the skin blood flow and skin temperature after intravenous infusion of thiopental coincided favorably with the first-order simulation model and, the second-order or higher factors are negligible when the transient phenomena are relatively brief [1,2]. However, the present results showed that in the epidural anesthesia using plain 2% mepivacaine, the simulation model did not correspond to the actual values. In the previous study, the time required for skin blood flow to plateau after barbituate infusion was within 3 min. Conversely, with the epidural anesthesia using plain 2% mepivacaine, it took more than 10 min to plateau. It is therefore, considered that the ramp function of the first-order system (composed of blood vessel-tissue-skin) in this relatively slow change, especially in epidural anesthesia, is not among the factors determining skin temperature.

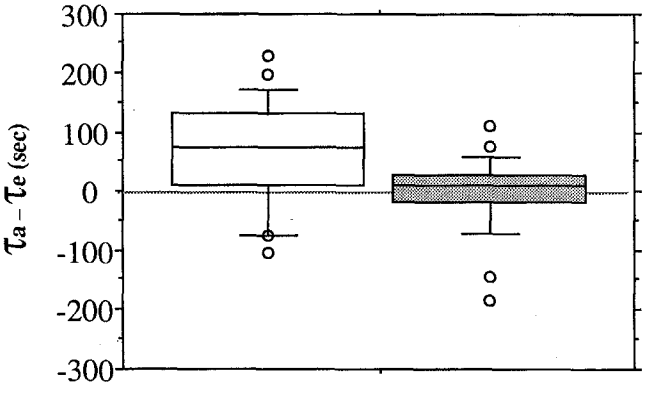

Fig. 3. Box plots of τ_a–τ_e in each patient. *open boxes*, nonalkalized group; *shaded boxes*, alkalized group. The (τ_a–τ_e) distributed closer to zero in the alkalized group than in the nonalkalized group

Cell bodies of the sympathetic nerve neuron are located in the intermediolateral cell column of the T1–L2 spinal segments. Efferent fibers of each spinal segment pass by way of the ventral root to a white ramus on to the paravertebral sympathetic ganglia. These fibers form a sympathetic chain from which each sympathetic nerve travels to several upper or lower segments. It was reported that sympathetic blockade is considered incomplete at the special segments during epidural anesthesia [8,9]. Further, incomplete sympathetic blockade during epidural anesthesia inversely decreases skin blood flow and temperature due to the decrease in systemic blood pressure [10]. In addition, the primary reason for the dissociation between the recorded and theoretical values during epidural anesthesia is considered to be the incomplete and slow onset of sympathetic blockade.

On the other hand, a better correlation between measured and theoretical values was obtained in the alkalinized group (Fig. 3). It is known that the onset of analgesia at the L5-S1 region during lumbar epidural anesthesia is slower than that in other regions [11]. However, the present study demonstrated that the L5–S1 region was very rapidly blocked by alkalinized mepivacaine. Indeed, the derived parameters in the alkalinized group were greatly reduced as compared to the nonalkalinized group (Table 2). Therefore, the rapid and complete onset of sympathetic blockade was achieved by alkalization of local anesthetics. This onset is considered to be responsible for the excellent correlation between the recorded and theoretical values.

In 1910, Gros [12] reported that the early onset of the neural blockades could be achieved by increasing the pH of local anesthetics. The mechanism of the effect of pH adjustment was clarified in the 1960s [13], and alkalinized local anesthetics have been applied in epidural anesthesia [14–16]. When pH was elevated from 6.35–6.9 to 7.20 by the addition of sodium bicarbonate, the time required for cutaneous analgesia in the S1 area was markedly reduced from 9.6–10.0 min to 1.92 min [16]. Moreover, Nickel et al. [11] reported that the speed of onset of pH-adjusted local anesthetics in the S1 area was significantly faster than a normal solution (3.6–4.0 *vs* 5.5–6.0 min) and that the time to complete the spread of analgesia in the S1 area was faster in the alkalinized local anesthetics than in the nonalkalinized solutions (9.6–10.0 *vs* 15.6–16.3 min). It has been reported that the plasma concentration of local anesthetics after epidural injection did not differ between nonalkalinized and alkalinized solutions, but the decrease of systolic pressure after injection of drugs occurred earlier in the alkalinized group. Further, the decrease in systolic pressure was larger in the alkalinized than the nonalkalinized group [17]. These results may indicate that alkalization of local anesthetics accelerates the sympa-

thetic blockade. Our results are consistent with these reports and provide further compelling evidence for the efficacy of pH adjustment.

This study has demonstrated that the mathematical model could not be applied to epidural anesthesia with nonalkalinized solution, but that concurrence found in alkalinized epidural anesthesia may be attributed to the rapid onset of sympathetic blockade by alkalinized mepivacaine.

Appendix

Finding function y(t) whose Laplace transform is

$$Y(s) = \frac{1}{\tau s^2}(1 - e^{-\tau s})\frac{1}{1 + Ts}$$

Let us denote the inverse Laplace transform of

$$G(s) = \frac{1}{1 + Ts}$$

and

$$U(s) = \frac{1}{\tau s^2}(1 - e^{-\tau s}),$$

by g(t) and u(t), respectively. Then referring to a table of Laplace transforms we find

$$g(t) = \frac{1}{T}e^{-t/T},$$

and

$$u(t) = \begin{cases} \frac{t}{\tau} & 0 < t \leq \tau \\ 1 & \tau < t \end{cases}$$

Since Y(s) is a product of G(s) and U(s), y(t) can be expressed by a convolution of g(t) and u(t), that is,

$$Y(t) = \int_0^t u(x)g(t - x)dx.$$

By performing this integration, we get

$$Y(t) = \begin{cases} \frac{t - T}{\tau} + \frac{T}{\tau} \cdot e^{-\tau/T} & (0 < t \leq \tau) \\ 1 + \frac{T}{\tau}(e^{-t/T} - e^{-(\tau/t)/T}) & (\tau < t) \end{cases} \quad (6)$$

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