Anesthesiology
57:167–171, 1982

Paradoxical Preservation of Neural Conduction by Lidocaine

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The interaction of glucose lack and local anesthetic on impulse conduction was investigated in rabbit vagus nerve. Glucose lack depressed the compound action potential 50 per cent in 47 ± 7 min (±SD, n = 5) and extinguished it in 69 ± 7 min. Lidocaine hydrochloride, 0.1 mmol/l (0.0027 g/dl), delayed the onset of inexcitability caused by glucose lack: 50 per cent depression required 85 ± 9 min, extinction required 131 ± 20 min ($P < 0.001$). The delay decreased with lower and higher lidocaine concentrations. Lidocaine also significantly decreased the potassium loss and sodium gain occasioned by 2.5 h of glucose deprivation. Thus, delayed extinction of excitability by local anesthetic in very low concentration may be due to decrease in permeability of the axonal plasma membrane not only to sodium but also to potassium ions. (Key words: Anesthetics, local: lidocaine. Ions: potassium; sodium. Membrane: nerve. Metabolism: glucose. Nerve: axon; conduction; metabolism; potential.)

WE RECENTLY DETERMINED that lack of glucose reversibly extinguishes conduction in the C fibers of excised rabbit vagus nerve within about 60 min.[1] Since clinical block of peripheral nerve usually is instituted with local anesthetic solutions devoid of glucose, it became of interest to examine the interaction of glucose lack and local anesthetic on impulse conduction. The study reveals that, in nerves deprived of glucose, subanesthetic concentrations of lidocaine paradoxically tend to preserve axonal excitability, possibly by impeding the steady leak of cations across the axonal membrane.

Methods

A cervical vagus nerve of a rabbit was incubated at 37.5–38°C in a closed chamber containing 50 ml of Ringer's solution bubbled with humidified 95 per cent O_2–5 per cent CO_2, and buffered with $NaHCO_3$ 24 mmol/l. The *p*H of the solution, measured at the start and end of incubation, ranged between 7.3 and 7.4. The nerve rested on an array of stimulating and recording electrodes, as previously described.[2] The time course of changes in the A and C components of the compound action potential was recorded photographically by raising the array out of the solution every 5 or 10 min and applying one stimulus supramaximal for A fibers, and a second stimulus 100 times stronger, supramaximal for C fibers, using 0.1-ms square pulses from a Grass S44® stimulator and stimulus isolation unit. The potentials were amplified and displayed on a Tektronix® type 532 cathode ray oscilloscope and photographed sequentially on Polaroid® film.

Group 1 nerves were controls incubated with 5 mmol/l (0.090 g/dl) glucose. Group 2 nerves were incubated with 5 mmol/l sucrose instead of glucose. Group 3 nerves were incubated with 5 mmol/l sucrose and 0, 0.005, 0.01, 0.1, 0.4, or 0.6 mmol/l lidocaine hydrochloride, one concentration per nerve. The nerve sheath remained intact during all incubations.

In additional experiments, pairs of nerves (n = 5) were incubated in Ringer's solution and 5 mmol/l glucose for 2 h, followed by further incubation with or without 0.1 mmol/l (0.0027 g/dl) lidocaine for a fixed 2.5-h period. At the end of this period the sheath of the nerve was removed, the desheathed core (composed of a single fasciculus) was weighed, and its K^+ and Na^+ content determined by flame photometry.

Significance of differences was evaluated by the two-tailed Student *t* test for unpaired samples.

Results

Delayed Extinction

Group 1. Control nerves (n = 8), incubated for 2–4 h in bicarbonate–Ringer's solution containing 5 mmol/l (0.090 g/dl glucose, manifested little or no change in the amplitude of the compound action potential.

Group 2. Nerves incubated in the Ringer's solution containing 5 mmol/l sucrose and 24 mmol/l sodium bicarbonate but no glucose (n = 5), showed extinction of A and C potentials at about the same rate (figs. 1 and 2). Therefore, only the amplitude of the C potential was measured. These nerves manifested 50 per cent depression of the action potential in 47 ± 6.3 min, and complete extinction in 69 ± 7 min (mean ± SD, n = 5; fig. 1 and table 1).

Group 3. Nerves incubated in solution lacking glucose but containing lidocaine 0.1 mmol/l (0.0027 g/dl) hydrochloride showed 50 per cent depression of the C-fiber potential in 85 ± 9 min ($P < 0.001$), and complete extinction in 132 ± 20 min ($P < 0.001$). Extinction of the A potential developed at about the same rate as that of the C fibers (fig 1).

The rate of extinction of the potentials was found to depend on the concentration of lidocaine in the glucose-

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Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington 98195. Accepted for publication February 2, 1982. Supported by Grant #1R01 GM 27678-01 from the National Institutes of Health, United States Public Health Services. Presented in part at the 1980 annual meeting of the American Society of Anesthesiologists.

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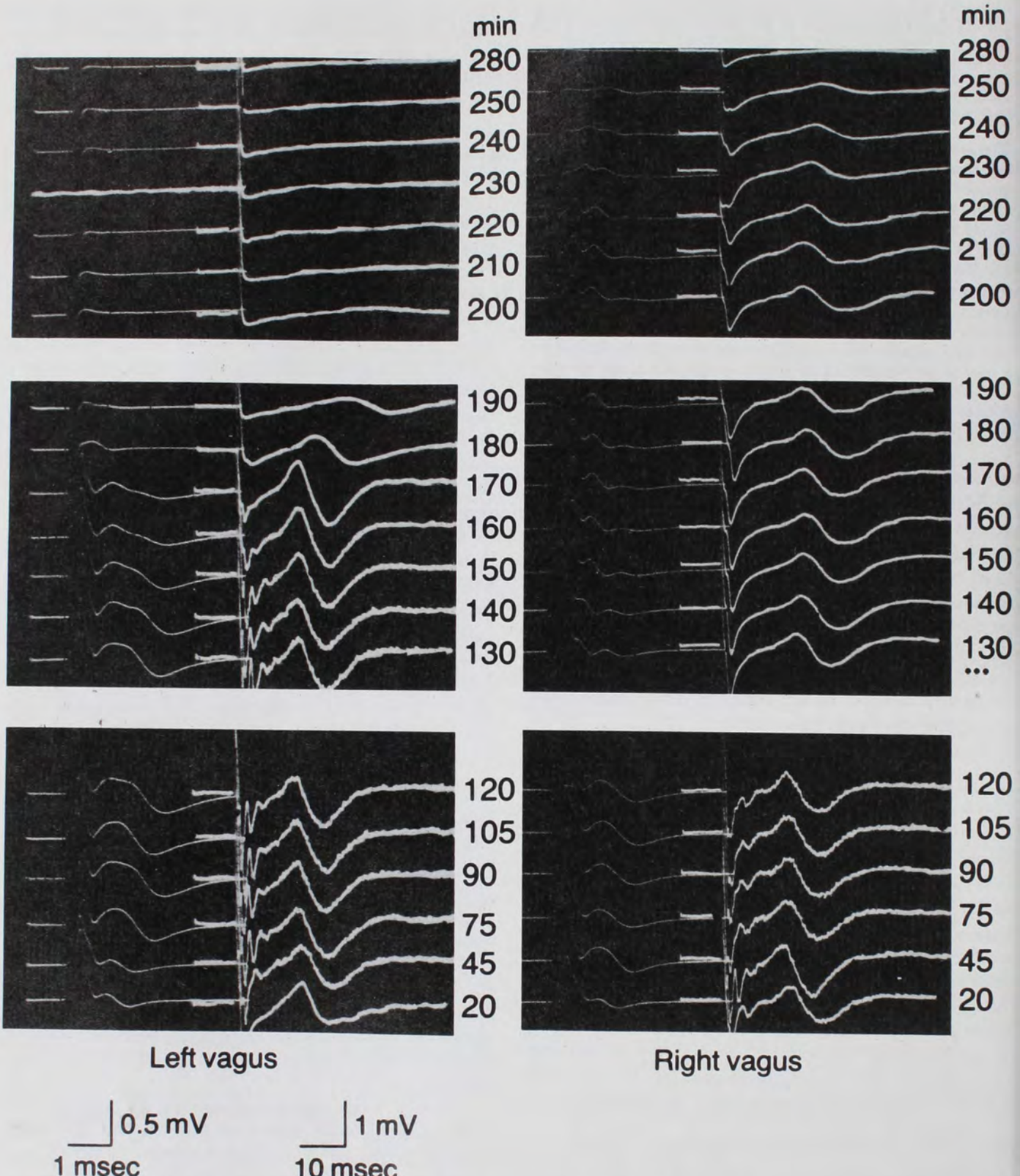

FIG. 1. Action potentials from a pair of sheathed vagus nerves during incubation in bicarbonate-Ringer's-glucose solution (lower panels) followed by bicarbonate-Ringer's-sucrose solution (middle and upper panels) which on the right included 0.1 mmol/l lidocaine. At each of the indicated time intervals the electrode arrays were raised out of the media, and two 0.1-ms stimuli were applied to each nerve, one stimulus being supramaximal (10 times threshold) for A fibers, the other 100 times stronger and supramaximal for C fibers. In each panel the fast, A-fiber potentials are recorded on the left; the slow C-fiber potentials on the right. Incubation time increases from the bottom moving upward. Note the paradoxically much slower rate of extinction of conduction in the nerve exposed to lidocaine.

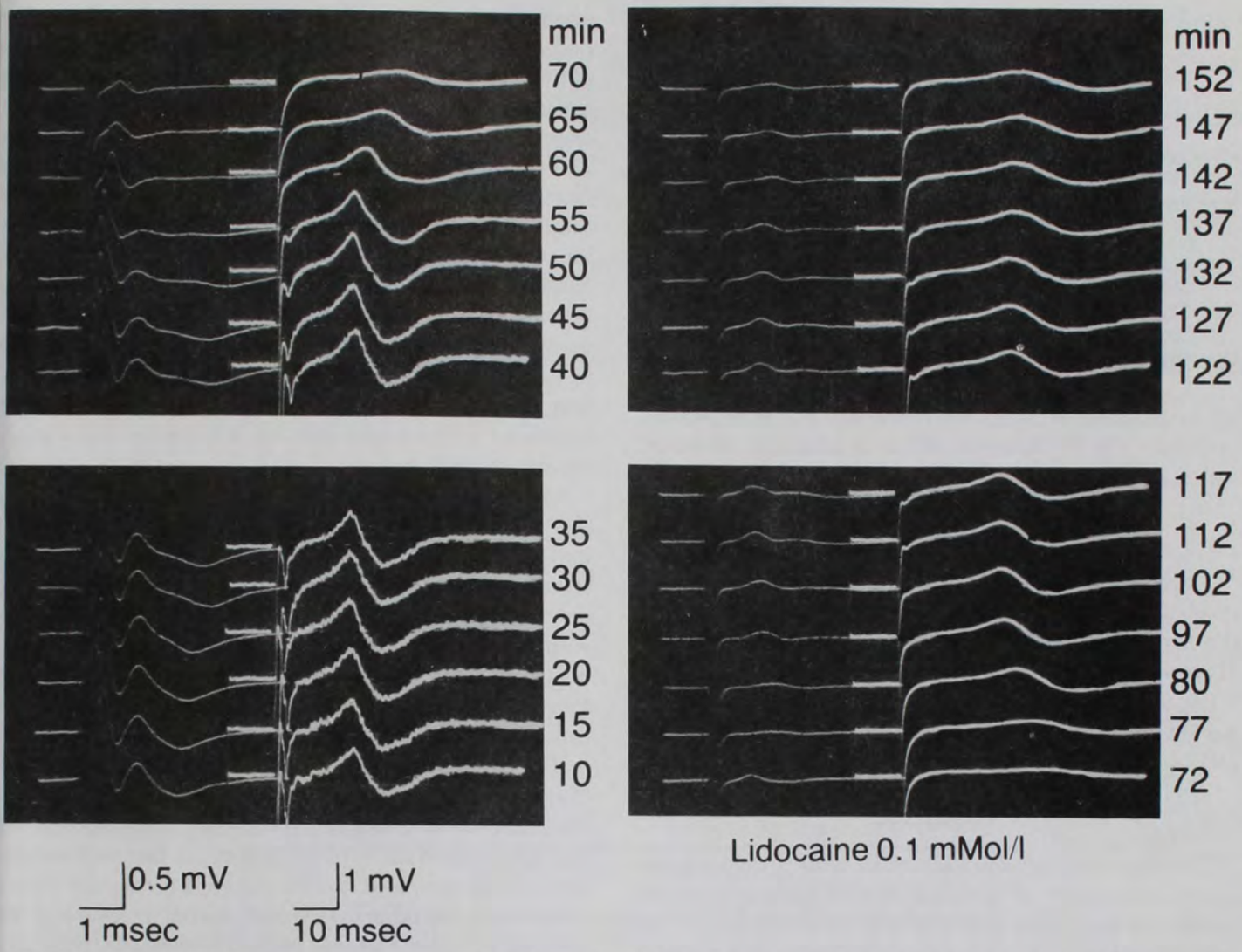

FIG. 2. Action potentials from a vagus nerve incubated in bicarbonate-Ringer's-sucrose solution. Glucose-deprived extinction of conduction in C fibers, observable in the left-hand panels, was partially reversed after the addition of 0.1 mmol/l lidocaine at the bottom of the lower right-hand panel. Note that incubation times indicated next to successive records increase from the bottom moving upward.

free solution (table 2), tending to increase with concentrations up to 0.1 mmol/l, and thereafter decreasing; with 0.6 mmol/l lidocaine, 50 per cent extinction required only 8 ± 3 min, approximately equivalent to the block time of the minimum blocking concentration C_m of de Jong.[3]

REVERSAL OF EXTINCTION

In four other experiments, after excitability had been extinguished by incubation in glucose-free solution, 0.1 mmol/l lidocaine was added. These nerves manifested 50 per cent recovery of the C potentials within 15 min

TABLE 1. Extinction Rate of C-fiber Potential in Glucose-free Incubations without and with Lidocaine (Means ± SD)

	50 Per Cent Depression (min)	Extinction (min)	n
Group 2			
No lidocaine	47 ± 6	69 ± 7	5
Group 3			
0.1 mmol/l Lidocaine	85 ± 9*	131 ± 20*	5

* $P < 0.001$.

TABLE 2. Effect of Lidocaine on Glucose-deprivation Depression of C fibers (Means ± SD)

Lidocaine (mmol/l)	50 Per Cent Depression Time (min)	n
0	47 ± 6	5
0.005	55, 65	2
0.01	80, 85	2
0.1	85 ± 9	5
0.4	48 ± 7	6
0.6	8 ± 3	5

TABLE 3. Potassium and Sodium Content of Nerve Cores after 2.5-h Incubation (Means ± SD)

	Potassium (mmol/kg)	Sodium (mmol/kg)	n
Glucose			
Group 1	55 ± 3	98 ± 5	8
Glucose-deprived			
Group 2			
Without Lidocaine	44 ± 4	110 ± 3	5
Group 3			
With lidocaine 0.1 mmol/l	52 ± 3*	101 ± 2†	5

* $P < 0.005$, and † $P < 0.001$ compared with glucose-deprived no-lidocaine incubations.

of the addition of lidocaine, followed by a slow, second extinction (fig 2). Recovery of the A potential, however, was minimal.

Nerve Core Electrolytes

Analysis of core electrolyte content at the end of the incubations indicated that in all glucose-free incubations, the nerves lost potassium and gained sodium (table 3). However, nerves incubated in the presence of 0.1 mmol/l lidocaine retained significantly more potassium and gained significantly less sodium than their counterparts incubated in the absence of lidocaine.

Discussion

The experiments summarized in table 1 demonstrate that development of inexcitability in glucose-deprived nerve was delayed by subanesthetic concentrations of the local anesthetic, *i.e.*, concentrations below 0.6 mmol/l (table 2).

Maintenance of axonal excitability requires that the ratio of intracellular to extracellular concentrations of cations, particularly Na^+ and K^+, remain within certain critical limits[4]; decrease in the ratio, as when potassium accumulates external to the axonal membrane, tends to depolarize the membrane,[5] and below a critical ratio excitability is lost. In the present study, extinction of excitability was due to glucose deprivation. The core electrolyte data suggest that lack of energy for the membrane pump allowed excess efflux of potassium and influx of sodium, causing the trans-plasma membrane gradients of these cations to decline, at least one of the gradients eventually falling below the value critical for excitability. The high sodium content of the core relative to potassium probably arises from the large size of the extracellular space in the vagus nerves of rabbits, estimated to amount to 60 per cent.[6] Thus, the sodium value tends to reflect the extracellular space, while the potassium value reflects the smaller size of the intracellular space. Bearing in mind that the perineurium has a low permeability to small cations,[7] two mechanisms to explain the observed paradoxical excitability-prolonging action of lidocaine may be considered: 1) lidocaine *increased* permeability of the perineurium to cations, and 2) lidocaine *decreased* permeability of the axonal membrane to cations.

Mechanism (1) would lower the concentration of cations in the extracellular compartment and maintain excitability by delaying the critical decrease in intracellular:extracellular cation concentration ratios. But if lidocaine had increased the permeability of the perineurium to cations, one would expect the nerves incubated with lidocaine to have lost more potassium than the nerves incubated without lidocaine. In fact, the reverse was observed (table 3).†

Mechanism (2) would maintain excitability by slowing the efflux of potassium out of or influx of sodium into the axons and delay the fall of the intracellular:extracellular cation concentration ratios to below the critical level. The observation that nerves incubated with 0.1 mmol/l lidocaine retained significantly more potassium and gained significantly less sodium than those incubated without lidocaine supports mechanism (2).

The reversal of extinction by the addition of lidocaine (fig. 2) may be explained along analogous lines. After the addition of lidocaine, continuing unhampered diffusion of potassium outward across the perineurium, together with slowed diffusion outward across the axonal membrane, temporarily effected partial recovery of the gradient across the axonal plasma membrane, with partial restoration of conduction. The effect on sodium influx was probably less important than the effect on potassium efflux, since transmembrane changes in the sodium concentration gradient are less critical to excitability than changes in potassium concentration gradient. Preliminary results with procaine suggest that the phenomenon may not be restricted to lidocaine.

The potassium-conserving effect of lidocaine in glucose-deprived peripheral nerve is evocative of a similar effect in ischemic dog brain, recently described by Astrup *et al.*[8] In the latter, the lidocaine dose was 160 mg/kg

† Dr. Bo van Deurs, of the Department of Anatomy, University of Copenhagen, kindly prepared and examined nine freeze-fracture replicas from two specimens of control nerves and two specimens of lidocaine-exposed nerves. Magnification of approximately ×100,000 did not reveal any differences in the granularity of the strands of the perineurial zonulae occludentes. Since zonula occludens tight junctions are known to restrict the movements of many molecular species across epithelia, the freeze-fracture observations tend to negate the idea that lidocaine relaxed perineurial restrictions on the movement of Na^+ and K^+.

(approximately 0.6 mmol/l), 'selected to be well above the convulsant level.' (The convulsant level in humans, 10 μg/ml of blood, is approximately 0.04 mmol/l.) In the present study, the paradoxical conduction preserving effect of lidocaine was detectable with concentrations below the convulsant level (table 2).

The author thanks Dr. Andrew M. Cairns for his excellent assistance.

References

1. Fink BR, Calkins DF: Role of glucose or potassium lack in nerve block. ANESTHESIOLOGY 55:172–175, 1981
2. Fink BR, Barsa J, Calkins DF: Osmotic swelling effects on neural conduction. ANESTHESIOLOGY 51:418–423, 1979
3. de Jong RH: Local Anesthetics, 2nd edition Springfield, Charles C Thomas, 1977, p 52
4. Katz B: Nerve, Muscle, Synapse. New York, McGraw Hill, 1966, p 67
5. Curtis HJ, Cole KS: Membrane resting and action potentials from the squid giant axon. J Cell Comp Physiol 19:135–144, 1942
6. Keynes RD, Ritchie JM: The movements of labelled ions in mammalian non-myelinated nerve fibres. J Physiol (Lond) 179:333–367, 1965
7. Krnjevic K: Some observations on perfused frog sciatic nerves. J Physiol (Lond) 123:338–356, 1954
8. Astrup J, Skovsted P, Gjerris F, Sørensen HR: Increase in extracellular potassium in the brain during circulatory arrest: Effects of hypothermia, lidocaine, and thiopental. ANESTHESIOLOGY 55:256–262, 1981