oxide was added to morphine–oxygen anesthesia. Cardiac output decreased 44 per cent, stroke volume 36 per cent, mean arterial pressure 22 per cent, and systemic vascular resistance increased 96 per cent with 50 per cent nitrous oxide. However, we observed changes at 10, 20, 30 and 40 per cent concentrations as well. Systemic vascular resistance increased 11 per cent at 10 per cent nitrous oxide, cardiac output decreased 10 per cent, mean arterial pressure decreased 4 per cent, and stroke volume declined 11 per cent. Each incremental change in nitrous oxide concentration led to further increments of change in the variables such that the extent of cardiovascular response became directly related to the nitrous oxide concentration. Since heart rate did not significantly change in our study, it appears that depression of cardiac output resulted from a decrease in stroke volume. Decreases in cardiac output and stroke volume at a given nitrous oxide concentration were two to three times the amounts of the observed decrease in arterial blood pressure.

These findings demonstrate that nitrous oxide can significantly reduce cardiac output during morphine anesthesia. This occurs even at low concentrations. While measurement of arterial blood pressures is routine during anesthesia, the magnitude of blood pressure changes caused by nitrous oxide is not necessarily as great as the change in cardiac output. This dissociation is not apparent, however, unless cardiac output and stroke volume are being measured. This suggests that when nitrous oxide is to be used in patients with minimal cardiac reserve, cardiac output or some other measure of cardiac function should be followed as a better index of the overall cardiovascular effects of the agent during morphine anesthesia. The advantage of using morphine should then be balanced against the positive contributions nitrous oxide is making to the maintenance of anesthesia.

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Spinal Hypalgesia and Analgesia by Low-frequency Electrical Stimulation in the Epidural Space

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Electrical stimulation of the brain by electrodes placed over the scalp can produce sufficient unresponsiveness to painful stimuli to permit surgical manipulations, and has been used with success in both animals[1] and man.[2] Electrical stimulation of the spinal cord also causes inhibition of cord function[3–5] and has been employed in management of pain.[6,7] Various types of current have been used for electronarcosis: 100–300-Hz rectangular pulses,[3,6,7] direct current,[4,5] and combinations of these.[7] However, when applied to the spinal cord, these currents often evoke muscular spasm and unpleasant sensations,[6,7] which have prevented wide clinical use of the technique in management of pain.

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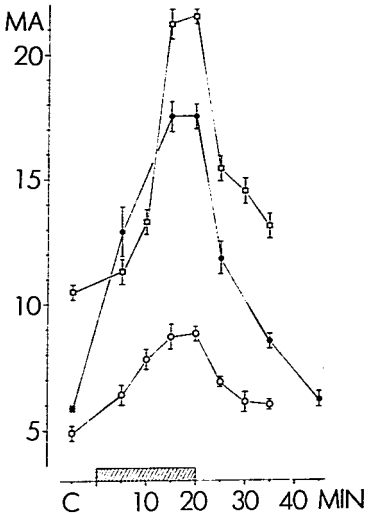

FIG. 1. Sequential changes in pain threshold expressed as peak current (ordinate) produced by the spinal cord stimulation (indicated by the shaded block at bottom) in three subjects. Note gradual increases and decreases in pain threshold.

We have been studying human electrospinograms recorded from the epidural space. During this study, we noticed that low-frequency and weak-intensity electrical stimulation of the human spinal cord epidurally produces analgesia or hypalgesia over a wide area of the body surface beyond the area innervated by the spinal cord segment under stimulation.

METHODS

Volunteers for this study were eight healthy young adults without neurologic deficit. Prior to the study, we explained the purposes of the study to each subject and obtained consent. On the day of study, the subjects arrived in the operating room fasting and without premedication. They were placed on an operating table in a lateral decubitus position for introduction of the electrodes into the epidural space at segmental levels from C5 to L3. The procedure for electrode placement in the epidural space, based on established methods of epidural anesthesia, has been described in detail.[8] Stainless steel wires, 125 μ in diameter and insulated to within 5 mm of the tip, were placed via a Tuohy needle into the anterior or posterior epidural space. A nonpolarizable silver needle was inserted into the adjacent supraspinous ligament. These electrodes were connected to a constant-current stimulator (Nihon Kohden MSE-3) through an isolation unit. The stimulus used was 5 Hz in frequency, 0.5 msec in duration, and 3.5–11.5 mA in intensity. Twitches of segmental muscles were caused, but they were weak and not unpleasant to the subjects. Positions of electrodes in the epidural space were estimated by observing twitches of segmental muscles and by monitoring evoked electrospinograms recorded with epidural electrodes in response to single-shock stimulation of an appropriate peripheral nerve.[9,10] Final confirmation of electrode position was made radiologically at the end of each study.

To assess the analgesic effect of spinal cord stimulation, the pain threshold was measured electrically in each subject. A pair of nonpolarizable silver needle electrodes was inserted subcutaneously 2 cm apart in an area of the trunk at the same level as the epidural cathodal electrode. These subcutaneous electrodes were connected to another constant-current stimulator (MSE-3). Bursts of 300-Hz square pulses were delivered through these electrodes. To determine pain threshold with this electrical stimulation, the current intensity was increased gradually to the point at which the subjects felt pain. The subjects were instructed to offer a sign when they felt pain, at which point peak intensity of the stimulating current was measured. This method of measuring the pain threshold was repeated ten times at each period, and the mean and standard error of the threshold current were calculated. Pain threshold measured by this method did not change significantly during 30–45 minutes of control studies prior to stimulation of the epidural electrodes. The segmental area and gross degree of the analgesic effect were

TABLE 1. Areas and Degrees of Analgesia in Eight Subjects 15 Minutes after the Start of Cord Stimulation

	Age (Years)	Electrode Position*		Area and Degree of Analgesia or Hypalgesia Tested by Pin-Prick		Pain Threshold Expressed as Peak Current (mA)	
		Cathode	Anode	Area	Degree	Control	15 Min
Subject 1†	22	P T10	A T10	T5–T10	Analgesia	—	—
Subject 2	22	P T12	R	—	—	7.0 ± 0.2	6.0 ± 1.0
		P T10	A T10	T3–T10	Hypalgesia	5.9 ± 0.1	17.5 ± 0.6 (S)
Subject 3	21	P L1	P C7	—	—	5.1 ± 0.2	5.9 ± 0.8
Subject 4	21	P L1	R	—	—	4.5 ± 0.2	4.6 ± 0.2
		P T12	R	—	—	4.5 ± 0.2	6.1 ± 1.0
Subject 5	21	P L1	A L2	T7–L1	Hypalgesia	5.5 ± 0.2	7.2 ± 0.2 (S)
		A L2	P L1	—	—	5.5 ± 0.2	5.3 ± 0.1
Subject 6	22	P C6	R	C6–S1	Hypalgesia	4.8 ± 0.4	7.8 ± 0.2 (S)
		P C5	R	C5–T11	Hypalgesia	4.9 ± 0.3	8.7 ± 0.5 (S)
Subject 7	22	P L1	R	T7–L1	Analgesia	10.5 ± 0.3	21.0 ± 0.6 (S)
		P T12	R	T4–T12	Hypalgesia	10.5 ± 0.2	14.7 ± 0.4 (S)
Subject 8	22	P L3	P T12	T10–L4	Hypalgesia	4.3 ± 0.1	6.8 ± 0.4 (S)

* A and P denote the anterior and posterior epidural space, respectively. R, an adjacent supraspinous ligament into which an electrode was inserted. S in parentheses represents a significant difference from control value ($P < 0.01$).

† Electric measurement of pain threshold in this subject not carried out.

also tested by the pin-prick method. When the subjects reported no pain in response to pin-prick or less pain than in other areas of the body, the area tested was considered to be analgesic or hypalgesic, respectively. Sense of touch was tested by tapping the skin lightly with a stick. Vibratory sense was tested by pressing an electric vibrator on the skin. Arterial blood pressure was measured by sphygmomanometry and pulse rate was recorded. Hemodynamic changes did not occur upon spinal stimulation except in one subject, in whom a slight increase in blood pressure (from 118/75 to 126/80 mm Hg) took place.

RESULTS

All subjects developed a pleasant "massage-like" feeling at the site of cord stimulation. The analgesic effect increased gradually as spinal cord stimulation continued, reaching a maximum in 15 minutes (fig. 1). After cord stimulation stopped, the analgesic effect remained for more than 15 minutes (fig. 1). Touch and vibration were not affected. Analgesic effects with approximate segmental areas, determined by the pin-prick 15 minutes after the start of the spinal cord stimulation, are summarized in table 1. Variable degrees of analgesia were demonstrated over a wide area of the body surface at or beyond the segment stimulated in six of eight subjects. The degrees and ranges of analgesia or hypalgesia were bilateral in these six subjects. The evoked electrospinogram and evoked responses in the skull following electrical stimulation of the posterior tibial nerve were not significantly changed by cord stimulation in three subjects in whom this was tested (Subjects 6, 7, and 8 in table 1).

DISCUSSION

These data indicate that low-frequency stimulation of the human spinal cord can produce hypalgesia or analgesia at the same segmental level and even beyond. The mechanism by which analgesia is achieved, however, remains to be defined. The analgesic effect seemed to originate in the segment of the cathodal electrode and project rostrally, except in one subject (Subject 6). Reversal of polarity between the electrode in the posterior epidural space and the reference electrode, without making the subjects aware of the change, led to a disappearance of analgesia within a few minutes in three subjects tested (Subjects 6, 7, and 8). This maneuver also decreased the segmental muscle twitches and the massage-like feeling. This might indicate that the analgesic effect originated in the

dorsal part of the cord. X-rays revealed that the tips of cathode electrodes lay approximately 3 mm from the sagittal plane in the posterior epidural space in the six subjects in whom hypalgesia or analgesia was obtained and beyond 5 mm in the two in whom no hypalgesia or analgesia was produced. This suggests that the median positioning of the stimulating electrode might be essential for production of the analgesic effect.

A direct current or a higher-frequency (100–1,000 Hz) pulsed current applied along or across the spinal cord has been found to have a narcotic effect in animals[3,5] and man.[6,7] However, the weak, low-frequency stimulation used in the present study has not previously been evaluated. A gradual increment and decrement in analgesia following cord stimulation in the present study suggests that the narcotic effect of the low-frequency stimulation may be ascribable not to the electric current itself[5] (conduction block) but to an indirectly activated effect. Melzack *et al.*[11] found that vigorous vibration raised the threshold for electric-shock pain. Melzack and Wall[12] have postulated a spinal cord "gate" as an explanation of this phenomenon. A similar mechanism might be involved in the analgesia or hypalgesia observed in the present study. However, the rostral projection and gradual increment and decrement of the analgesic effect could not be explained by this "gate" theory. The lack of change in large-fiber sensation and in evoked responses during or immediately after cord stimulation may lead to the assumption that the functional organization of spinal cord is well preserved during cord stimulation. In connection with this, it should be noted that all the subjects in the present study reported that they felt a pleasant sensation during cord stimulation.

This method of producing analgesia might be applied to management of intractable pain or production of surgical anesthesia.

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