

Intestinal Neuromuscular Function after Preservation and Transplantation¹

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While it is well known that prolonged preservation of the intestinal graft causes severe mucosal damage after transplantation, little is known about the effect on neuromuscular function. The entire small intestine of adult hound dogs was flushed and preserved with cold lactated Ringer's solution and autotransplanted either immediately ($n = 6$) or after 24 hr ($n = 6$). Animals undergoing sham operation ($n = 4$) were used as a control. Fasting motility and the response of the intestinal smooth muscle and enteric nerves to bethanechol (100 $\mu\text{g}/\text{kg}/0.5$ hr, iv) and cisapride (0.5 mg/kg, iv) were determined by a multiple strain gauge method on Postoperative Days 2, 4, 7, 14, 21, and 28. Compared to the control, immediately transplanted grafts and those preserved for 24 hr developed delayed reappearance of migrating myoelectric complexes (MMC), hypercontractile activity, and reduced response to bethanechol and cisapride administration. Animals in the preservation group developed more abnormal fasting motility after transplantation, but responses to bethanechol and cisapride stimulation were not markedly different from those of the immediate group. The reappearance of MMC occurred 3 weeks postoperatively in the preservation group compared to 2 days in the immediate group. The results of our study indicate that intestinal dysmotility is augmented in prolonged-preservation grafts compared to those with brief preservation. The dysmotility was transient and normalized 3 to 4 weeks after surgery. Preservation and reperfusion injury to the neuromuscular system of intestinal grafts are reversible and are attenuated by simple hypothermia. © 1996 Academic Press, Inc.

INTRODUCTION

Transplantation of the intestine has been known to cause dysmotility [1-3]. While intestinal dysmotility

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occurred in a modified model of intestinal autotransplantation, where enteric blood flow was uninterrupted [4], dysmotility was further augmented if the graft received even a brief ischemic insult [1]. Ischemia and reperfusion damage to the enteric nervous system and the muscle layer have been speculated to be the primary cause of intestinal dysmotility in these models [5]. Prolonged intestinal preservation causes severe mucosal damage (hemorrhage, sloughing, and transmural neurosis) to occur after transplantation [6, 7]. No studies have examined the effect of prolonged ischemia and preservation on intestinal neuromuscular function.

In this study, we investigated the effect of preservation on the posttransplant function of the enteric nervous system and the muscle layer of the intestinal graft by a multiple strain gauge method. Since the nervous system is highly sensitive to ischemia, we hypothesize that mucosal layer necrosis [6, 7], caused by ischemia/reperfusion, would accompany profound nervous injury and result in irreversible intestinal dysmotility. Abnormalities of the nervous system and the muscle layer after preservation and transplantation were analyzed by studying the response to cisapride and bethanechol, respectively. In addition, we used an intestinal autotransplantation model to avoid the confounding effects of rejection and immunosuppressive agents on intestinal motility [8].

MATERIALS AND METHODS

Animals. All studies were performed on adult mongrel dogs of either sex, each weighing between 18 and 25 kg. The animals were given oral kanamycin sulfate (1 g/day), fed with a low-residue diet for the 5 days before surgery, and fasted from the evening prior to surgery. The dogs were anesthetized with intravenous thiopental sodium (25 mg/kg) for induction and maintained with halothane, nitrous oxide, and oxygen by positive pressure mechanical ventilation. Arterial blood pressure, blood gases, and electrolytes were monitored throughout the study.

Operative procedures. Canine autotransplantation was performed in a similar fashion as Lellihei *et al.* [9] originally described and as modified in our laboratory [10]. Briefly, after exposure of the abdominal cavity through a midline laparotomy, the small intestine from the ligament of Treitz to approximately 10 cm proximal to the

ileocecal valve was isolated on a vascular pedicle consisting of the proximal superior mesenteric artery (SMA) and the superior mesenteric vein (SMV). After removing the intestine, the graft vasculature and lumen were each perfused with 1 liter of modified cold (4°C) lactated Ringer's solution containing 3000 U of heparin and 0.5 g of kanamycin. The graft was autotransplanted either immediately ($n = 6$) or after 24 hr of cold preservation in lactated Ringer's solution ($n = 6$). Transplantation of the graft was accomplished by end-to-end anastomoses of the graft and host SMA and SMV, followed by restoration of intestinal continuity by a two-layer, end-to-end anastomosis of the jejunum and the ileum.

Eight strain gauge transducers (Star Medical Co., Tokyo, Japan) were suture-fixed to the gastrointestinal serosa at the following sites: gastric antrum (5 cm proximal to pylorus), duodenum (5 cm distal to pylorus), jejunum (J1, 15 cm; J2, 30 cm; and J3, 45 cm distal to duodenojejunal anastomosis), and ileum (I1, 45 cm; I2, 30 cm; and I3, 15 cm proximal to ileoileal anastomosis). The strain gauge transducers' lead wires were brought out of the abdomen through the flank and tunneled subcutaneously to the midscapular region where they were exteriorized. A protective jacket (Star Medical Co., Tokyo, Japan) was placed on each dog to protect the lead wires.

In a separate group of four control animals, the strain gauge transducers were prepared similarly to those of the animals subjected to autotransplantation. Intestinal continuity and neural innervation remained intact in these animals.

All animals (control and experimental) received 1–2 liters of lactated Ringer's solution containing 5% dextrose for 3–5 postoperative days. One gram of intramuscular cefamandol was given daily for 5 postoperative days. Dogs were allowed to drink and eat from the day following transplantation. A meat-based low-residue liquid meal was given for the first 3 days after surgery, followed by a low-residue solid meat meal until Postoperative Day (POD) 7. Animals were fed standard kennel food thereafter.

Measurement of intestinal motor activity. The animals were fasted for 18 hr before each measurement of intestinal motor activity. The strain gauge transducers were attached to a Gould TA 4000 recorder (Gould Inc., Cleveland, OH), and motor activity was recorded and stored digitally. Fasting intestinal motility was monitored 2, 4, 7, 14, 21, and 28 days after transplantation. After obtaining 6 hr of spontaneous motor activity recording, bethanechol (100 $\mu\text{g}/\text{kg}/0.5$ hr, iv), which is a cholinergic antagonist and a direct stimulator of intestinal smooth muscle, and cisapride (0.5 mg/kg, iv), which enhances the release of acetylcholine from nerve endings, were given intravenously (separated by an interval of 2 hr) to evaluate the physiologic properties of smooth muscle and nerves of the intestine.

Motor activity was measured by manually analyzing the printed recordings. Phasic contractions lasting a minimum of 30 sec with an amplitude of greater than 30 g and a frequency greater than 10 contractions per minute were defined as a burst of contractions (BOC). Migrating motor complexes (MMCs) were defined as cyclic and propagating contractions that had three typical phasic patterns. Strong repetitive phasic contractions lasting more than 4 min that propagated aborally but lacked the typical MMC pattern were defined as "phase 3-like contractions." Bursts of contractions, occurring during the last 3 hr of baseline recording, were analyzed for their total duration and frequency. The time to recovery and the frequency of propagated phase 3-like contractions were observed during the entire baseline recording period. Large, individual contractile waves that propagate aborally and had two to three times higher amplitude than MMC contractions were defined as giant migrating contractions (GMCs).

Contraction bursts, as a result of drug administration, were analyzed by averaging the contraction amplitude and frequency over a 20-min period beginning 10 min after starting the bethanechol infusion and for 10 min after the cisapride bolus. To avoid irrelevant expiratory excursion, contractions with amplitudes less than 15 g were excluded from the analysis.

The occurrence of the MMC was noted, and the duration of the individual components (phases 1, 2, and 3) and propagation velocity of phase 3 were measured at the jejunal sites.

Statistical analysis. All values were expressed as means \pm standard error of the mean. Statistical comparisons between data from

the control animals and each group of animals with autotransplanted jejunum were performed using ANOVA with Scheffe's probability testing by post hoc analysis to determine the significance of differences between mean values. Differences were considered significant if the P value was less than 0.05.

RESULTS

General Condition after Transplantation

Control and autotransplanted animals tolerated the surgical procedures well. Of special note, no animals in the 24-hr preservation group were lost due to graft failure.

Watery diarrhea was seen during the first 2 to 3 weeks after intestinal autotransplantation in both groups, of which the preservation group had profuse diarrhea. However, stool consistency improved and stool volume decreased progressively thereafter in both groups. Four weeks after transplantation, body weight loss in the preservation group was higher, $20.2 \pm 3.1\%$, than in the immediate group, $13 \pm 2.8\%$, but the difference was not statistically significant.

Fasting Motor Activity

MMCs were observed in the intestine of all control dogs 2 days after sham operation. Although the period of MMC cycling and the duration of various phases of the cycle were more variable than in the control, MMCs were recorded 2 days after transplantation in the immediate group (Fig. 1A). In contrast to control and immediately transplanted dogs, none of the preservation group animals showed any motor activity at POD 2. Propagated phase 3-like contractions appeared at POD 21 and 28 (Table 1) in only one-half of the preservation group animals. The remaining preservation group animals had simultaneous or rapid propagated cluster contractions, lasting 1 to 2 min (like minute rhythm), which was seen in all preservation animals before POD 21 (Fig. 1B). The incidence of phase 3-like contractions on POD 21 and 28 in the preservation group was significantly less than that of the control group, but was not different from the immediate group.

The total duration of phase 1 activity was shorter in the immediate group than in the control group for all dates of the measurement, but only statistically significant at POD 14 and 21. In contrast, the duration of phase 2 activity was longer in the immediate group versus the control at all dates of the measurement, but only statistically significant at POD 21.

Figure 2 illustrates postoperative changes in the duration and the frequency of the BOC at the jejunum and the ileum of the control and transplanted animals. Bursts of contractions, including phase 3-like contractions, were observed in both intestinal segments as early as POD 2 in the control group and the immediate group, while contractile activity was scarce in the jejunum and absent in the ileum of the preservation group during this early postoperative period. However, the duration and frequency of BOC in both transplantation groups abruptly increased after POD 4 and reached

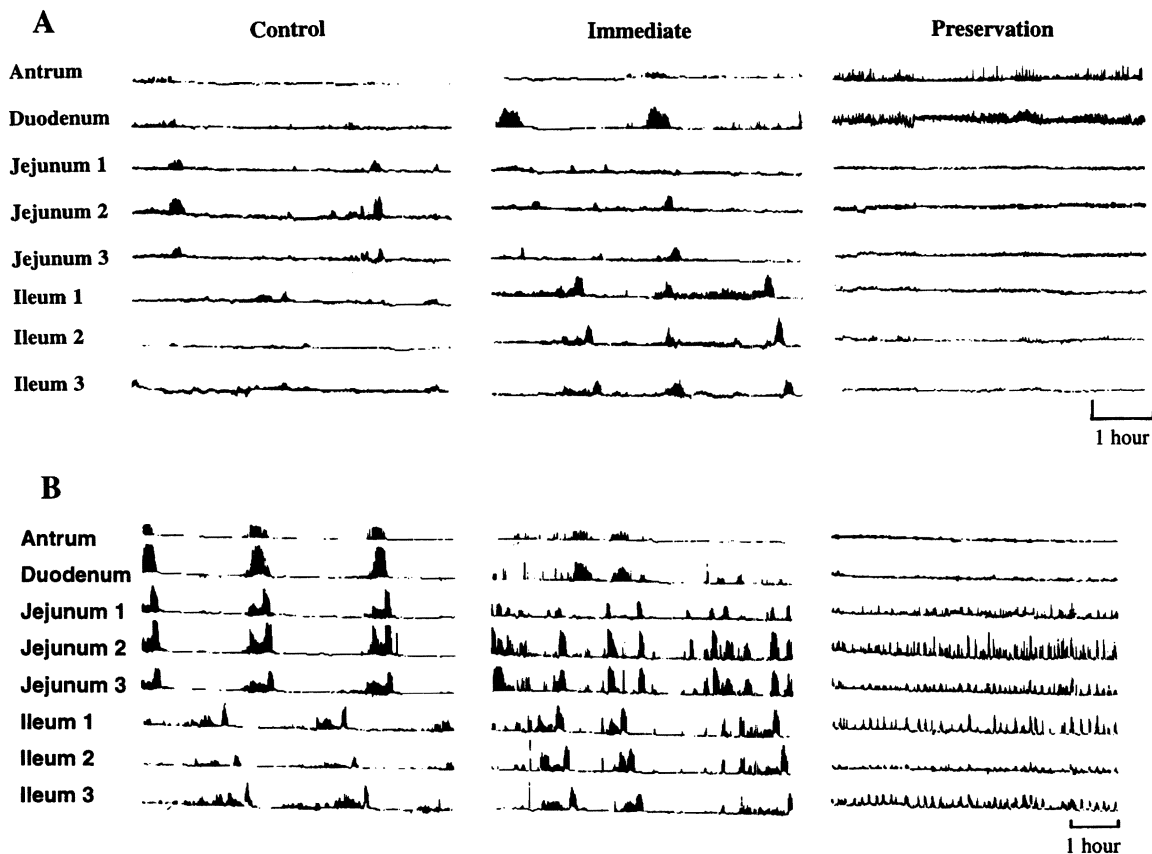


FIG. 1. (A) Examples of the three experimental groups on the fasting pattern of motility at POD 2. Note that MMCs were already observed in the control and the immediate transplanted jejunoleum, but the preservation group showed no motor activity. (B) Examples of the three experimental groups on the fasting pattern of motility at 7 POD. The control dog shows a regular cyclic MMC pattern. Although the period of MMC cycling and the duration of various phases of the cycle were more variable, MMCs were seen in immediately transplanted jejunoleum. In contrast to the previous two groups, the preservation group showed simultaneous or rapidly propagated clustered contractions without MMC.

their highest levels at POD 7. These changes were more prominent in the preservation group animals.

Response to Drug Stimulation

Although the mean amplitude of contractions in response to bethanechol tended to be lower in the immediate and preservation groups than the control group for 2 to 3 weeks after transplantation, there was no statistically significant difference between the two transplant groups. Likewise, the frequency of BOC in immediate grafts and preserved grafts in response to bethanechol was markedly less than that of the control for 1 week after operation; however, there was no statistical difference between the immediate and preservation groups (Fig. 3).

The mean amplitude of contractions in response to cisapride gradually increased and stabilized 2 weeks after transplantation equally in both groups at both intestinal segments. No evident differences were seen among the three groups, except for lower amplitude of the immediate group at POD 4. Similarly, contractile frequency of the jejunum after cisapride injection showed no statistical difference among the three groups. The frequency of contractions in the ileum of

the immediate group was significantly lower than that of the control and preservation groups. This finding may be attributed to the frequent occurrence of GMC, since GMC was always accompanied by a quiescent phase of various lengths (Fig. 4). Giant migrating complexes appeared at all times exclusively in the ileum of the control group and four to five times more often in the immediate group after cisapride injection. In the preservation group, GMCs were not observed before POD 7, but they increased progressively after POD 14 (Fig. 5).

DISCUSSION

Clinically, the University of Wisconsin solution is the current standard for preservation of intestinal grafts; however, in this study lactated Ringer's solution was used because we and others demonstrated marked histological and biochemical abnormalities of the mucosal layer using this solution [6, 7], and we tried to determine the reversibility of graft dysmotility under the most critical experimental circumstance, with 24-hr preservation.

Our results demonstrated that enterectomy and isch-

TABLE 1
Incidence of Propagated Phase 3-like Contraction^a

Postoperative day	Control		Immediate		Preservation	
	Jejunum	Ileum	Jejunum	Ileum	Jejunum	Ileum
2	0.54 ± 0.03	0.38 ± 0.02	0.08 ± 0.01*	0.11 ± 0.01*	0*	0*
4	0.54 ± 0.02	0.46 ± 0.02	0.36 ± 0.02	0.22 ± 0.02	0***	0*
7	0.54 ± 0.02	0.42 ± 0.02	0.75 ± 0.02	0.33 ± 0.01	0***	0***
14	0.54 ± 0.02	0.50 ± 0.02	0.64 ± 0.01	0.42 ± 0.02	0***	0***
21	0.50 ± 0.02	0.42 ± 0.02	0.39 ± 0.02	0.28 ± 0.02	0.11 ± 0.01*	0.08 ± 0.01*
28	0.50 ± 0.02	0.42 ± 0.02	0.33 ± 0.02	0.37 ± 0.01	0.08 ± 0.01*	0.17 ± 0.02

^a Number of phase 3/hr.
* *P* < 0.05 versus control.
** *P* < 0.05 versus immediate.

emia associated with intestinal transplantation induced marked abnormalities in the motility of canine intestinal autografts. Both the immediately transplanted grafts and the 24-hr preserved grafts had abnormal MMC, delayed reappearance of MMC, hypercontractile activity, and reduced response to bethanechol and cisapride administration compared to those of the control intestines. Initially, prolonged preservation of intestinal grafts, which caused mucosal necrosis after revascularization, was thought to eradicate the recovery of motility

function due to the vulnerability of the enteric nervous system to ischemia. Although fasting motility was more abnormal during an early postoperative period, the preservation group exhibited responses essentially similar to those of pharmacological stimulations as the immediate group, and one-half of the animals regained a normal MMC pattern during the third postoperative week. Hypothermia with a simple electrolyte solution appears to have provided better protection for the neuromuscular system of the intestinal grafts.

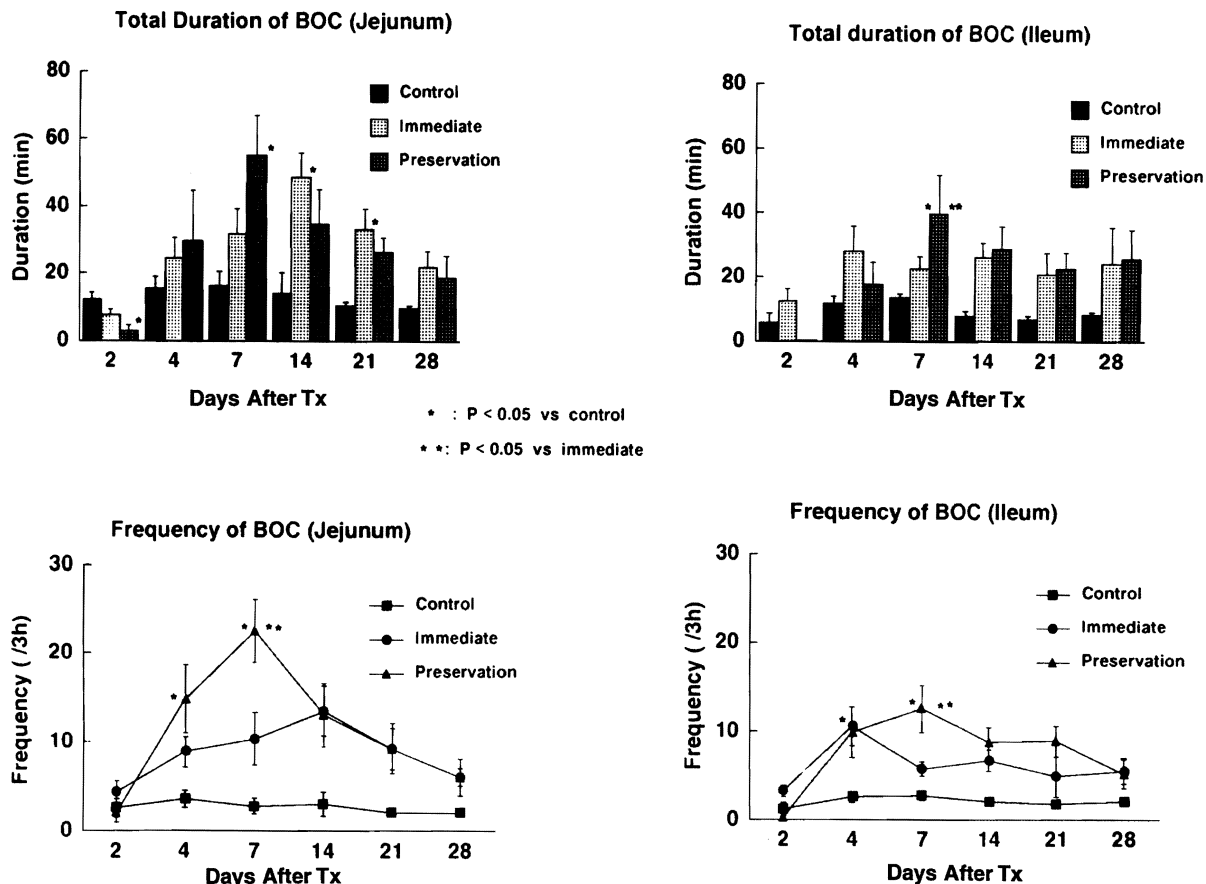


FIG. 2. Duration and frequency of BOC in the transplanted jejunioleum at the indicated day after transplantation. **P* < 0.05 versus control; ***P* < 0.05 versus immediate.

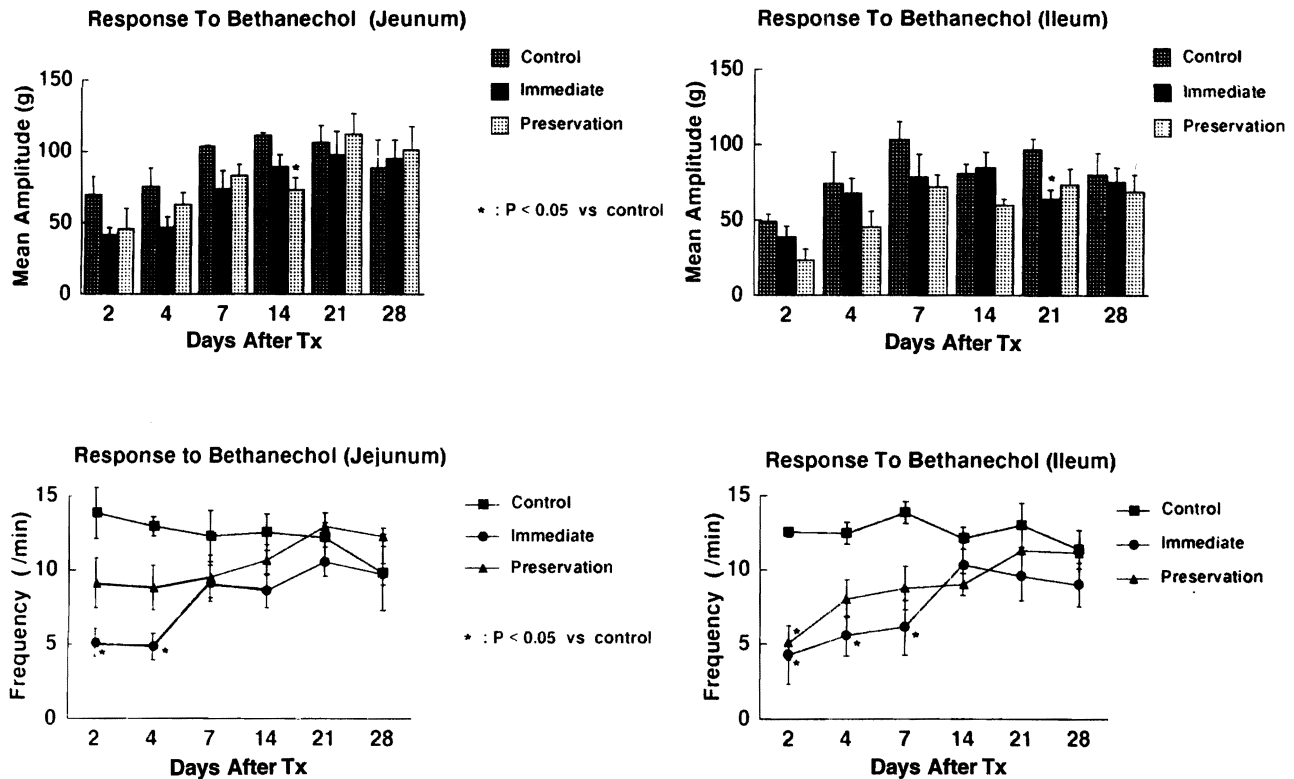


FIG. 3. Response to bethanechol injection of the control, immediate, and preservation groups. * $P < 0.05$ versus control.

Migrating motor complexes occur periodically in the fasting state in most nonruminant mammalian gastrointestinal tracts and play an important role for cleansing food residue and debris from the enteric lumen. After Szurszewski identified the MMC in 1969 [11], a number of investigators have tried to elucidate the mechanisms of initiation and propagation of the MMC. Three major mechanisms have been advocated, including extrinsic neural control, circulating hormonal control, and intrinsic neural control. However, it is now well established that transection or disruption of the extrinsic nervous system by vagotomy [12, 13], by total sympathectomy [14], or by superior and inferior mesenteric ganglionectomy [15] alters [16] but does not abolish MMC cycling in the small intestine. It is also evident that MMCs occur without a corresponding increase in plasma concentration of motilin or other peptides [17]. Itoh *et al.* [18] and Ormsbee *et al.* [19] reported that MMCs in the Thiry–Vella loop occur independently of the MMCs in the remainder of the small intestine. Small intestinal segments divided by transection and reanastomosed also generate their own MMC cycles independent of other segments [20, 21]. It has been reported that bolus injection of atropine (anticholinergic antagonist), hexamethonium (ganglionic blocking agent), and tetrodotoxin (neuronal transmission blocking agent) via an intra-arterial catheter to the intestinal segment blocked phase 3 propagation at the perfused site [22]. Thus, these observations suggest that the initiation and propagation of the MMC are under intrinsic neural control, which is inherent to the enteric nervous system in the intestinal wall.

Prolonged preservation and subsequent reperfusion appear to functionally suppress the inhibitory neurons of the intrinsic nervous system which are involved in MMC initiation in the intestinal wall. In contrast to early resumption of the MMC in control intestines and in the immediate group grafts, the reappearance of the MMC, or propagated phase 3 contractions, was delayed until the third postoperative week in the preservation group. Wood first proposed the hypothesis that the intestinal smooth muscle is maintained in a state of inhibition, regulated mainly by inhibitory transmitters which are continuously released from nonsympathetic inhibitory neurons within the enteric nervous system [23]. Later, Wood confirmed the theory by studying myogenic activities after atropine and local analgesic treatment [24]. He described that the myogenic activity induced by these agents was due to removal of inhibitory control of the muscle by interrupting nervous inhibitory transmission within the pathways. Our findings with canine intestine are consistent with those reported by Taguchi *et al.* in an *in vitro* study using rat jejunal segments [25]. Rat intestines, stored with Euro–Collins solution for 24 hr, showed spontaneous contractile activity, pharmacological responsiveness, and excitatory innervation of intestinal smooth muscle, but had temporary impairment of intrinsic nonadrenergic inhibition. In their report, inhibitory activity returned 8 days after surgery, compared to 3 weeks in our experimental model. The discrepancy between the two experiments may result from the use of a different species, a different experimental model, or a different preservation solution.

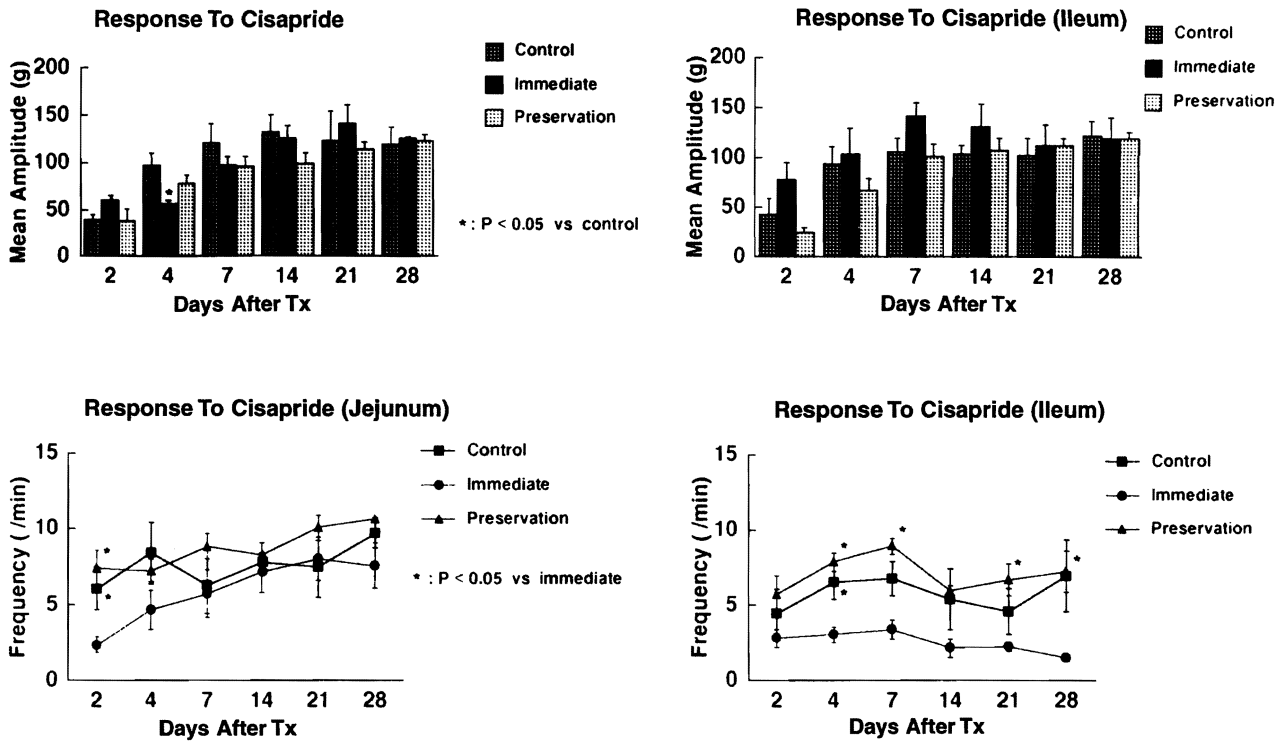


FIG. 4. Response to cisapride injection of the control, immediate, and preservation groups. * $P < 0.05$ versus control; * $P < 0.05$ versus preservation.

Functional and reversible suppression of the intrinsic nervous system of the intestinal wall by prolonged preservation and reperfusion was also confirmed with the response of the intestinal grafts to cisapride administration. The mean amplitude and frequency of intestinal contractions after cisapride administration in the preservation group were not much different from those of intact intestines and those of the brief preservation grafts. Unexpectedly, the frequency of the immediate group remained rather low, less than that of the preservation group, particularly at the ileal segment. Irrespective of the duration of graft preservation, the intestines of both transplantation groups generated similar amplitude and frequency of contractions in response to bethanechol administration, indicating that the functional capacity of the muscle layer in preserved intes-

tines is not much further impaired than that of immediately transplanted intestines. Since the action of cisapride on the electrical behavior of myenteric neurons is explained by facilitation of cholinergic transmission (increased acetylcholine release from the myenteric plexus) [26, 27], the experiment with cisapride administration in our study suggests two potential events: first, that the cholinergic excitatory nervous system is essentially intact even after 24 hr of cold preservation and transplantation; and second, that the coincidence of the appearance of GMCs after cisapride injection and the appearance of propagated phase 3 contractions on POD 21 reveals the recovery of intrinsic nervous function. Sarna investigated the characteristics of spontaneously and pharmacologically induced GMCs in the small intestine of conscious dogs [28]. Although the mechanism of initiation and the precise physiological role of GMC are unclear, the more frequent incidence of GMCs in the immediate group than in the control group, and the appearance of GMCs in the preservation group after possible recovery of intrinsic inhibition, suggests that the GMC may be associated with the extrinsic (adrenergic) and intrinsic (nonadrenergic) inhibitory system.

The results of this study indicate that dysmotility of the intestinal graft after prolonged preservation and transplantation is reversible and that the integrity of the canine intestinal smooth muscle and nervous system and their functions are rather well preserved by hypothermic storage with a simple electrolyte solution. The study also suggests that prolonged preservation damages the inhibitory enteric nervous system, and

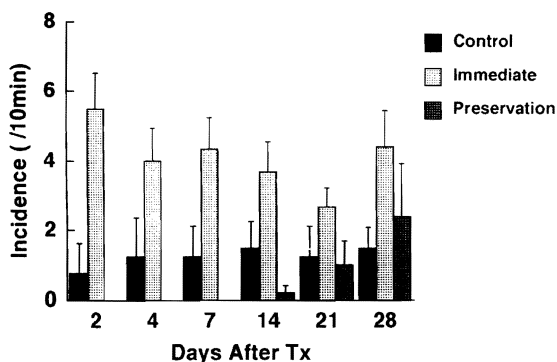


FIG. 5. The incidence of occurrence of giant migrating complexes after cisapride injection.

this impairment does not recover until at least 2 or 3 weeks after transplantation. Morphological analysis by neuroimmunohistochemical techniques is needed to determine the extent of nervous damage and the process of recovery, which would support our functional observation, and is currently under investigation.

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