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CERVICAL SPINAL CORD TRANSECTION (SCT) INCREASES GASTRIC COMPLIANCE IN ANESTHETIZED RATS

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Abstract: *Spinal cord injury (SCI) can markedly alter the autonomic nervous system's functions. It immediately causes autonomic and somatic hypo- or arreflexia, a state known as spinal shock. SCI determines the enhancement of two gastric reflexes that appear in normal conditions: the receptive and adaptative reflexes. Furthermore, this study also tried to evaluate the causes that led to such modifications: either vagal control, nitric oxide (NO)-pathways or intestine-intestinal reflexes. Male Wistar rats (N=25) were subjected to laminectomy (Sham group) or laminectomy + complete Spinal Cord Transection (SCT), between C7 and T1 vertebrae under anesthesia (SCT group). Before the surgery, the rats had water and food ad libitum; after the surgery, rats were fasted for 24 hours, still having access to water. The next day, all animals were subjected to a catheterism of their right carotid artery, a tracheostomy and a flexible balloon introduction down to the stomach's fundix region, also under anesthesia. Rats were connected to a Power-Lab® system, via a pressure transducer (in order to measure the arterial pressure – MAP - and the heart rate - HR), and to a modified Plethysmometer (in order to measure the fundical gastric volume - GV variation). Vagal control was studied via cervical vagotomy; NO-mediation - via NO synthesis inhibitors (L-NAME); intestinointestinal reflexes - by using laxatives (Lactulone). Statistical analysis revealed, in some cases, that GV is significantly ($p<0.05$) augmented in SCT rats (2,4±0,09; 3,1±0,05; 3,7±0,06 ml) than in Sham (2,2±0,12; 2,9±0,12; 3,3±0,15 ml). Nevertheless, MAP and HR, were subsequently lower ($p<0.05$) in SCT (63,5±21,1mm Hg; 227,1±25,2 BPM) than in the control group (88,2±14,4mm Hg; 427,0±19,2 BPM). In summary, the increase of GV in SCT, seems to involve vagal pathways and/or NO-mediation, but still not neglecting the colic-gastric reflexes.*

INTRODUCTION

The stomach behaves as a reservoir for the meal ingested; after mixing the contents of the meal, the organ pumps its contents via the pylorus into the small intestine for further digestion. The motor behavior is significantly different for the distinct anatomical parts of the stomach. Thus, the walls of the fundus and of the proximal part of the gastric body are involved in tonic contractions, while the distal part of the gastric body, the pyloric antrum and the pylorus itself are responsible for implementing phasic contractions.(1)

The gastric compliance phenomenon consists of the ratio between the intragastric volume and its pressure. This is a propriety relatively characteristic for the fundus of the stomach. Normally, while the gastric tonus diminishes, the volume rises and the pressure is maintained in constant parameters – this is the normal Compliance propriety of the stomach. Gastric compliance is modified in several conditions: physiological and pathophysiological. After ingesting food, intragastric pressure (IP) does not augment, even if the volume raises, mainly because of the *receptive relaxation reflex* (a vagally mediated dilatation of the proximal stomach that diminishes its tonus). Furthermore, even if food ingestion is continued, IP does not remain constant, because the adaptative reflex intervenes (the stomach's volume augments, but not because of the distention, but because of the continuous downfall of the tonus).

The impact of spinal cord transection (SCT) over the gastrointestinal (GI) system has been reported to determine: delayed large bowel transit(2) colon and anorectal functional alterations.(3) In rats, experimental studies have also shown that a decrease of the distal colon's motility is also present.(4) Even so, there are few and controversial studies (in both clinical and experimental studies) that address the modifications that appear in upper GI tract, in spinal cord injury (SCI).(5,6)

After affecting the autonomic nervous system, SCI immediately causes autonomic and somatic hypo- or a- reflexia, a state described as spinal shock. This phenomenon is not completely understood despite the intense research carried out in the last century.(7) The loss of supraspinal sympathetic inhibition is responsible for the majority of phenomena that appear.

Still, the behavior of the stomach brings up a lot of controversy. Recent experimental studies show that acute cervical spinal cord transaction decreases gastric emptying and intestinal transit of liquid in awaken rats.(8)

To our knowledge, there are few studies that address the physical modifications that appear at the gastric level.(9)

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Thus, variations of the volume and of the gastric compliance have not been reported in SCT experimental animals.

AIM

The aim of this study is to identify whether there indeed are gastric compliance modifications in SCT experimental animals, and furthermore, to establish which are the mechanisms responsible for the modifications that appear, not taking into consideration the loss of sympathetic supraspinal inhibition.

MATERIALS AND METHODS

1. Animals. General protocol of SCT.

Experiments were performed on 25 adult male Wistar rats, weighing 295-366 g. All surgical procedures and animal treatments were conducted in accordance with the "Guide for the Care and Use of Laboratory Animals" [DHEW Publication no (NIH) 85-23, Bethesda, Maryland, USA]. The animals were allowed access to food and water before the first phase of the surgery. *SCT-group animals* were first anesthetized with a mix of ketamine and xilasine 2% (0,006 mg/body weight g) administrated intramuscular (i.m). Dorsal cervical laminectomy was performed; the interspinous ligament was carefully dissected, exposing the seventh cervical (C7) and first thoracic (T1) vertebrae via a midline dorsal incision. SCT was completed using a fine cut scissor. *Sham- control group animals* also underwent dorsal cervical laminectomy, but without subsequent interspinous ligament dissection and cord transaction. The bleeding was minimal and usually stopped in 10-15 seconds. Complete hemostasias was completed via layer-by-layer suture using cotton, catgut or vicryl linen. The completeness of the SCT was verified by careful inspection of the lesion with the aid of a 10x lens coupled to an optic light. A complete transaction was confirmed in all cases and further clinical parameters (paraplegia, lack of nociception and somatic reflexes below the lesion, hyperrefflexia of the tail, as well as urinary retention) – indicating completeness of the SCT was observed after recovery from anesthesia. Immediately after SCT, the rats were allowed to recover on a warm pad and were closely monitored for signs of respiratory or circulatory distress. Typically, in the majority of the cases, the rats were awake and mobile (using their forelimbs) 20 min after surgery. Rats that exhibited grooming and exploratory behavior when removed from their cage were considered healthy spinal rats.(10) Animals were placed in separate cages and maintained with water *ad libitum*, but without access to food, until performing further experimental protocol, 24 hours later. The cages were placed in a ventilated, dry room that facilitated the preservation of the animals' nictemeral rhythm. Urinary bladder emptying in SCT-animals was accomplished by manual hypogastric compressions three to four times a day.(11) Nevertheless, haematuria and sub-cornean hemorrhage were signs that confirmed the complete SCT, in SCT-group animals.

After 24 hours, the animals were completely anesthetized using Urethrane 20% (1,2g/kg), injected intraperitoneal (i.p). Infrahiodian incision was done, in order to facilitate the approach of the right common carotid artery, the jugular vein and of the vagus nerve; the artery and nerve were surgically separated. The carotid artery and jugular vein were ligatured and had a poliethylen catheter (PE-50, 29 gauge-G caliber tubes) filled with saline and heparine (500U/ml) and introduced downwards. This maneuver was done to help measure the mean arterial pressure (MAP) and heart rate (HR) of the animal, and to obtain a venous pathway. Next, the animals were submitted to a tracheostomy to ensure free breathing.

2. Measurement of the gastric volume

After surgery, a balloon catheter [outside diameter (OD): 1,5 mm; inside diameter (ID): 2 mm; 20 cm in length] was introduced *per os* and positioned in the proximal stomach. The balloon with a volumetric capacity of about 3 ml, was obtained from surgical-glove fingertips. The opposite and of the catheter was connected to a three-way valve and then to the bottom of a U-shaped glass reservoir (volume: 30 ml; ID: 2,5 cm). The reservoir was equipped with an electronic volume sensor coupled to a plethysmometer (model 7140, Ugo Basille, Comerio, Italy). A syringe was connected to the valve to fill the balloon, the catheter and the reservoir with a pre-warmed (37^oC) standard ionic solution (0,3 ml Imbebiente BBC 97, Ornano, Italy – and 99,7 ml of 45 mg% NaCl). The reservoir liquid level was settled 4 cm above the animal's xyphoid appendix. Gastric balloon-volume changes transmitted through the vessels systems to the reservoir were continuously displayed by the plethysmomether. Gastric volume (GV) values (in ml) were recorded every 1 out of 10 min of monitoring (12) (figure no. 1).

GV variations were studied by gradually modifying the height of the reservoir (from 4 cm above the xyphoid process, to 8 cm and then to 12 cm), thus artificially augmenting the intra-gastric pressure (from the basal value of 4 cm H_2O, to 8, and 12 cm H_2O, respectively). The modification of the reservoir's height was done every 10 minutes; recording of the GV continued. Owing to its large volumetric capacity, the reservoir functions as a barostat – distending the stomach under constant pressure. Therefore, the measurements of GV indicate gastric compliance.(12)

Some of the animals (N=15), were subjected to three different protocols after the surgical steps were done.

Protocol 1: 5 of the animals were connected to the plethysmomether for 10 minutes at basal height (4 cm above the xyphoid process) and then cervical bilateral vagotomy (CBT) surgically was performed (*SCT + vagotomy group*). Recordings of the GV continued with the modifications of the hight of the reservoir.

Protocol 2: Another group of 5 animals each was connected to the plethysmomether for 10 minutes at basal height, and then a nitric-oxide (NO)-synthesis inhibitor (N-nitro-L-arginine methyl ester: L-NAME, 3mg/kg) was administrated via the jugular vein catheter (*SCT + L-NAME group*). GV was continuously recorded at all reservoir's height modifications. [13]

Protocol 3: 24 hours before the first surgery, the last group of 5 animals was pre-treated with a laxative (Lactulone – 2ml/300 g) – *SCT + Lactulone group*. Surgery and GV measurements were done according to previous description.

3. Cardiovascular parameters

A continuous MAP was obtained by connecting the common carotid catheter to a pressure transducer (P 100B, Narco-Biosystems, Houston TX, USA), coupled to a polygraph (Mark IV, Narco-Biosystems, Houston TX, USA). MAP values, were recorded in the mm Hg scale every minute. At every 10-min interval, the chart speed was increased from 0.025 to 1 cm/s during 1 min to obtain the HR values (measured in beats per minute – BPM).

After the experiment, the animals were subjected to a medial laparotomy to verify whether the balloon is still in the fundus of the stomach. The volume of the catheter was aspirated and measured in a graduated cylinder (10 ml). This was done in order to observe whether there had been any variations of the balloon volume during the experiment and if the balloon had any leaks. Finally, the anesthetized animals were sacrificed by an i.v. injection with a saturated KCl solution.

4. Statistical Analysis

Haemodynamic and GV data were obtained from monitoring each animal for 10 min at every pressure increase. The global results for each separate group were calculated as arithmetical mean of the results obtain from each individual

animal.

Next, the results were expressed as Mean ± SEM and graphically represented as columns. The Unpaired t-Student test was used to compare the differences in GV between Sham-control group and SCT-group, SCT+Vagotomy group, SCT+L-NAME group and SCT+Lactulone group. The comparison was made for every pressure value (4, 8 and 12 cm H_2O respectively) recorded at every 10 minutes.

Differences between MAP and HR at the various groups implied in the experiment were interpreted using the sum between the arithmetical average and the standard error deviation of the values measured after the modification of the pressure (after 4, 8 and 12 cm H_2O). Values of p lower than 0.05 were considered statistically relevant.

RESULTS

Figure no. 2 shows that the GV has significantly increased in the SCT group after elevating the gastric pressure up to 8 and 12 cm H2O (3.13±0.04; 3.72±0.05ml) vs Sham group (2.87±0.1; 3.27±0.12 ml; p<0.05), respectively. Furthermore, table no. 1 shows that basal MAP are lower in SCT-group (63.5±21.1 mm Hg) in relation to Sham (88.2±14.4 mm Hg, p<0,05); basal HR values at SCT-group animals were also subsequently lower (227.1±25.2 BPM), than in Sham-control group (427±19.2 BMP; p < 0.05). Mean arterial pressure and heart rate, did not increase in direct correlation with the augmentation of the gastric volume.

Figure no. 1. Schematic representation of the plethysmometric method utilized for gastric volume measurements.

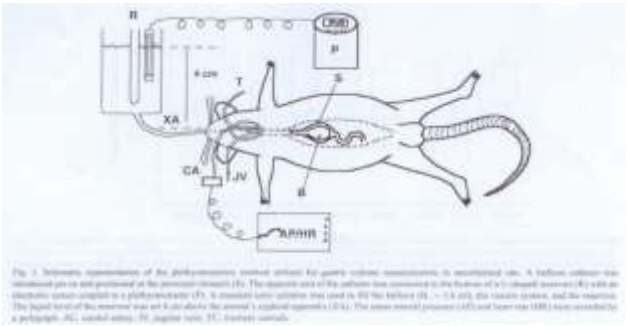


Figure no. 2. The effect of spinal cord transection over the gastric compliance in anesthetized rats: the graphical differences between Sham and SCT -groups

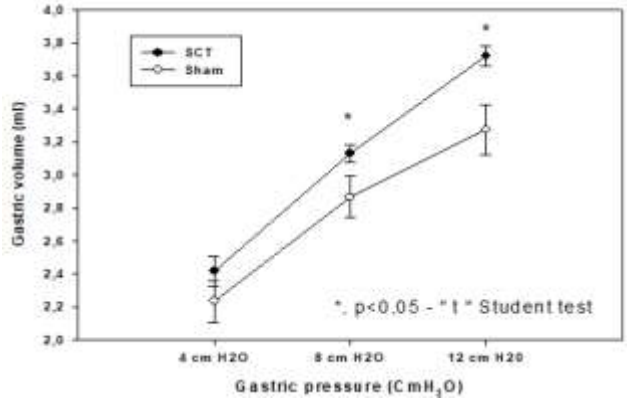


Figure no. 3 demonstrates that cervical bilateral vagotomy (SCT+vagotomy group) decreases GV at each gastric pressure modification (1.79±0.13; 2.22±0.14; 2.47±0.14 ml; p<0.05) vs. Sham- control group (2.4±0.1; 2.87±0.1; 3.27±0.12 ml). Table no. 1, shows that MAP values, measured at a 4 cm H_2O pressure, increase after vagotomy (97.1±24.9 mm Hg) in correlation to SCT-animals (65.8±22 mm Hg); HR does not modify after vagotomy.

Figure no. 3. The effect of spinal cord transection over the gastric compliance in anesthetized rats the graphical difference between Sham – and SCT+Vagotomy- groups

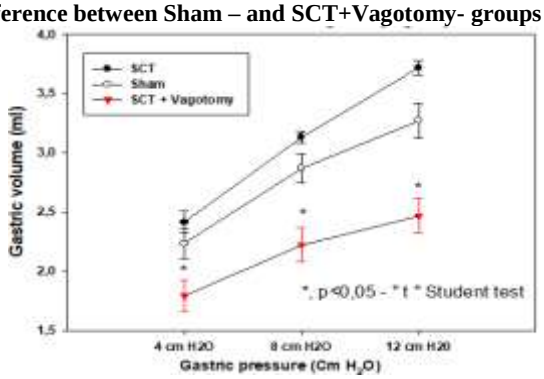
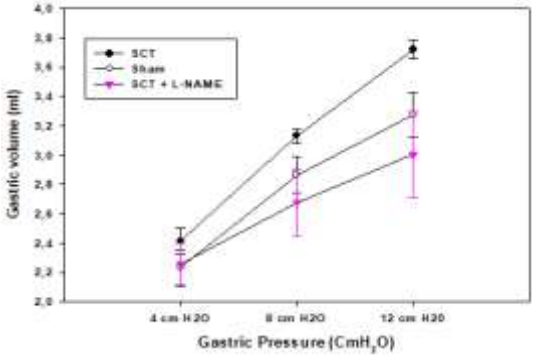


Figure no. 4 presents that L-NAME pre-treatment prevents the augmentation of GV values in SCT animals (2.26±0.14; 2.7±0.22; 3.0±0.29 ml – pre-treated SCT animals vs. 2.4±0.07; 3.13±0.04; 3.72±0.05ml – non-treated SCT animals; p<0.05) at every pressure increase. The results from Table 1, show that L-NAME pre-treatment increases MAP values, measured at 4 cm H_20 pressure (70.8±9.5 mm Hg, p<0.05) without modifying the HR in correlation to non-treated SCT animals.

Figure no. 4. Effect of spinal cord transection over the gastric compliance in anesthetized rats the graphical difference between Sham- and SCT+L-NAME- groups



In Figure no. 5 one can observe that Lactulone pre-treatment also prevents the augmentation of GV values in SCT animals (2.44±0.07; 2.78±0.08; 2.96±0.16 ml; p<0.05) vs. non-treated SCT animals. Moreover, Table 1, shows that Lactulone-treated animals present an increased MAP – at a 4 cm H_2O pressure (80.3±23.0 mm Hg), still without a HR modification.

Figure no. 5. The effect of spinal cord transection over the gastric compliance in in anesthetized rats: the graphical difference between Sham-and SCT+Lactulone-groups

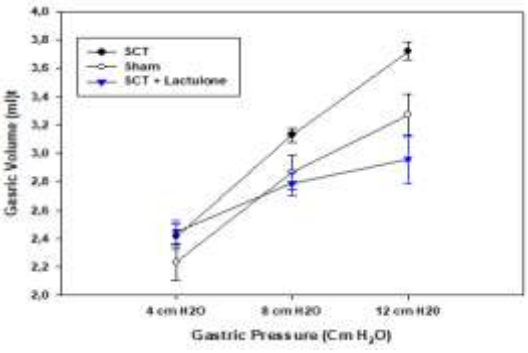
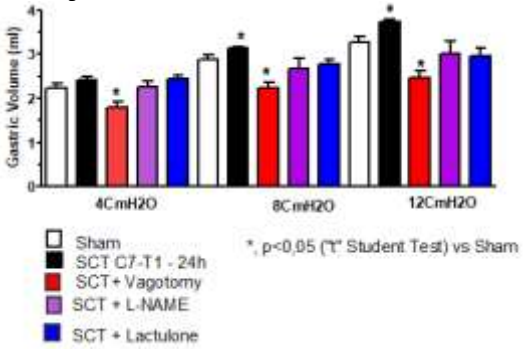


Table no. 1. Variation of the arterial pressure and the heart rate

	MAP (mm Hg)				HR (BPM)			
	Basal	4 cm H2O	8 cm H2O	12 cm H2O	Basal	4 cm H2O	8 cm H2O	12 cm H2O
LAMINECTOMY (Sham)	88,2±14,4	86,4±17,6	85,2±14,2	92,5±20	427,0±19,2	422,3±23,3	398,5±12,3	380,2±20,2
SCT	63,5±21,1	65,8±22	70,8±21,2	71,5±21,5	227,1±25,2	237,7±33,0	222,4± 25,4	214,7±28,2
SCT + VAGOTOMY	74,1±19,9	97,1±24,9	105,5±23,5	100±21	253,3±70,1	236,8±56,3	225,1±45,8	217,3±43,9
SCT + L-NAME	53,4±14,8	70,8±9,5	76,9±15,8	65,3±23,4	270,2±87,8	231,2±41	203±23,8	185,4±23,3
SCT + LACTULONE	72,1±20,2	80,3±23,0	81,7±21,7	81,6±20,4	184,1±20,9	218,4±20,4	243,9±32,2	250,5±56,8

The same statistically relevant results ($p<0.05$) can be observed in the columnar graphic presented in figure no. 6. The figure also presents the global result of the experiment: a comparison between al the experimental groups included.

Figure no. 6. The effect of spinal cord transection over the gastric compliance in anesthetized rats



DISCUSSIONS

SCT decreases the basal adrenergic activity in both humans and experimental animals, not only during the spinal shock phase, but also subsequently, when the autonomic hyperreflexia is fully established.(11) This could therefore indicate the predominant involvement of vagal pathways in the inhibition of gastro-intestinal (GI) motility and in gastric evacuation (GE) after SCT.(14) At the SCT experimental animal, so, without sympathetic control, the receptive and adaptative reflexes increase, thus determining the increase of the GV and of the compliance. Subacute and acute SCT decrease GE, intestinal and GI transit of liquid in awake rats(15); the decreased physical activity after SCT could also contribute to the inhibition of the GI motility.(15) All of these, cumulated, could consist in the primary, brute response of the body to SCT. In humans conflicting data about the effects of SCT on the motility and volumetric modifications of the upper GI tract are available: delayed GE of liquids or solids have been reported(6,16-21) and subsequently questioned.(20,21) A possible explanation for these discrepancies is the significant variation in age, sex and interval after injury, pattern and injury mechanism in human studies.(15) These variations were minimized in the present study since we utilized male rats with similar age and weight and the pattern of the SCI can be easily reproduced and standardized in experimental rats.

In addition to decreased basal adrenergic activity, the lack of supraspinal control over the sympathetic centers, after SCT also leads to inappropriate sympathetic firing after visceral stimulation, such as bladder/colonic distension, causing autonomic hyperreflexia. In fact, autonomic hyperreflexia elicited by gastric distension was considered to be the explanation for GE delay in patients with SCI.(16) The parasympathetic control over the stomach, mainly done by the vague nerve, consists augmenting the distention of the fundical region (intragastric volume growth) and inhibiting GE.

To the best of our knowledge, this is the first report in experimental animals, describing the direct, subacute and acute effect of cervico-thoracic SCT over the gastric compliance, and furthermore, tries to identify some of the causes that lead to this alteration. The main reasons upon which we considered to study the gastric compliance phenomenon is because it controls not only the normal appetite, but it also regulates the level of GE, encountered in normal subjects. The question raised is what happens with the phenomenon under the auspices of total cervico-thoracic SCT. After performing SCT, an increase in GV was noticed; the only remark here could be made in relation with the pressure at which the GV augmentation was registered: since the basal value of the fundical pressure is 4 cm H_2O, and the values of 8 and 12 cm H_2O can be reached only in experimental situations or in isolated physiological states (e.g.: ingestion of effervescent liquids), these results are relevant mainly for the study of SCT and the repercussions it causes.

Since GV determines a growth of the gastric compliance in SCT animals, we have tried to determine what the mechanism that leads to this modification is. So, because of the fact that the stomach lost most of its sympathetic control via SCT, we took into consideration the fact that it is mainly under vagal control, and thus, we preformed CBT, in order to cut down the parasympathetic direct control. After surgery the results registered concluded that the loss of vagal control determines a dramatic decrease of GV, (also of the compliance), significantly lower than the normal values and slightly under the values of the SCT-group.

Because CBT is a non-specific, surgical measure that interrupts all vagal fibers, the use of L-NAME facilitates the inhibition of specific parasympathetic non-cholinergic vagal fibers. NO-mediation is responsible with the relaxation of smooth muscle fiber, thus, the use of a NO-synthetase inhibitor is justified to follow the response of the gastric musculosa, and its impact over GV and volume.(22) Experimental results infirm the hypothesis upon which NO-mediation is directly related with the augmentation of GV in SCT, but we could not neglect the fact that NO-mediation can be a cumulative factor, together with others that determine the increase of gastric compliance in SCT. The inhibition of NO-pathways via pre-treatment with L-NAME is a measure that counteracts the GV/compliance increase in SCT animals.

Since SCT causes facilitation of the intestine-intestinal, entero-gastric colonic-gastric reflexes, accumulation of feces and decrease in stool output in experimental animals (23), (because there is a sudden lack of modulation from the central nervous system above the level of injury), we have taken into consideration the administration of Lactulone – a laxative-, to try to prevent the exaggeration of these phenomena and of their impact over the growth of GV/compliance. Experimental results confirm, as in the case of NO-pathways, that entero(colonic)-reflexes are not directly responsible with the increase of GV, but could consist in a cumulative factor that facilitates the alteration. Thus, inhibition of entero(colonic)-reflexes via laxative pre-

treatment could be a short term treatment to acute modifications that appear in SCT in relation with GV.

We also observed that MAP and HR levels were significantly decreased directly after cervical SCT, in agreement with previous results.(24) Particular mentions need to be brought regarding MAP values, measured at a 4 cm H_2O pressure which present an increase after vagotomy and after L-NAME pre-treatment, which could mean either the intervention of other vegetative reflexes or an accentuation brought to the spinal shock situation – in case of the CBT, either a loss of smooth vascular muscle relaxation – in case of L-NAME pre-treatment, respectively. [V] The increase of MAP in Lactulone pre-treatment registered at 4 cm H_2O is considered miscellaneous.

One clinical application of the experiment could consist in the evacuation of the colon in SCI patients, either via an enema, either via laxative administration, in order to try preventing the excessive augmentation of the GV and thus creating a suitable environment for oral food ingestion and stimulation of the GI motility. L-NAME treatment or other NO-Synthetase inhibitors are not indicated in clinical treatment, mainly because they intervene over the well-functioning of other smooth muscles in the body.

CONCLUSIONS

In summary, the experiment itself is a phenomenon study of SCT; the results registered show that GV increases determining a sequential increase of gastric compliance in complete SCT. For this modification, the responsible factors are: the lack of sympathetic supraspinal control, the acute response of the parasympathetic system (which has no antagonic mechanism), out of which, the NO-pathways play an indirect role, and the entero(colonic)-gastric reflexes - which cannot be ruled out - also with a cumulative indirect role. The increase of gastric compliance explains why GE and GI motility are on delay in SCT animals and vice-versa. Further studies could try to identify whether the main cause of GV augmentation is located at the level of the stomach (pylorus), at the level of the duodenum or even at the level of the colon. Also, Propanolol pre-treatment or other parasympathetic specific or non-specific inhibitors could be taken into consideration to observe the alterations of GV in SCT.

Similar studies, suggest that cervical spinal cord injury (CSCI) can lead to esophageal dysfunction and increase the risk of aspiration (Mendelson syndrome). Also, the CSCI has a direct effect on dynamic function of the pharynx and upper esophageal sphincter (UES).

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