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THE MOTOR EFFICACY OF THE ARTIFICIAL COLONIC PACEMAKER IN COLONIC INERTIA PATIENTS

Ahmed Shafik [1], Olfat El-Sibai [2], Ali A. Shafik [3], Ismail Ahmed [4]

[1] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, [2] Department of Surgery, Faculty of Medicine, Menoufia University, Shebin El-Kom, [3] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo , [4] Department of Surgery and Experimental Research, Faculty of Medicine, Cairo University, Cairo, Egypt

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1. ABSTRACT

We have recently demonstrated that the colon possesses at least 4 pacemakers which presumably generate electric waves and that colonic pacing evokes electric activity in colonic inertia. We tested the hypothesis that electric waves produced by artificial colonic pacing in colonic inertia patients may initiate colonic motilitiy and effect evacuation. 17 patients with constipation due to total colonic inertia were divided into 2 groups: 10 (age 45.6 ± 6.3 years, 7 women) in the study group and 7 (age 43.7 ± 5.8 years, 5 women) as controls. 7 healthy volunteers were included in the study. Colonic pacing was tested at 2 sites of pacemakers: mid-transverse colon and colosigmoid junction. A stimulating electrode was hooked to the colonic mucosa at the pacemaker site and 2-3 recording electrodes distally to it. Healthy volunteers showed resting electric waves in the form of pacesetter and action potentials which increased significantly on colonic pacing. Inertia patients exhibited no basal electric activity. Colonic pacing in the study group evoked electric waves and caused expulsion of small volume balloon. Balloon distension at pacemaker site produced mass movement of balloon, while away from pacemaker site step-wise movement. In conclusion, colonic pacing evoked electric waves in colonic inertia patients and effected balloon expulsion. We postulate that the pacemaker generates electric waves which spread along pacemaker branches that are composed of interstitial cells

of Cajal and nerve fibers of the enteric nervous plexus and effect colonic mass contraction. Ex-pacemaker stimulation presumably leads to local activation of interstitial cells of Cajal and segmental step-wise contraction.

2. INTRODUCTION

Colonic inertia is a cause of chronic constipation. It is a disorder of colonic motility and may be partial or total (1-10). Previous studies have shown that the colon exhibits electric activity in the form of slow waves or pacesetter potentials (PPs) and fast activity spikes or action potentials (APs) (11-18). The PPs were monophasic with a negative deflection. The APs followed, or were superimposed on, the PPs and were represented by negative deflection. They occurred randomly, did not follow each PP and were coupled with elevated colonic pressure (16-18). Other studies have shown that the electric waves are transmitted through smooth muscles of the gut and are partially controlled by intrinsic and extrinsic colonic innervation (19,20).

Colonic electric activity is considered to regulate colonic motility (14-18). The association of elevated colonic pressure with the APs points to an involvement of these waves in the motile activity (14-18). On colonic distension the AP frequency and colonic pressure increased (16-18). It is thus assumable that disorders of colonic electric activity impair colonic motility. This is evidenced in the electrocolograms recorded for the various pathologic lesions (17). In these conditions the frequency, amplitude and conduction velocity of the electric waves are believed to be below the required thresholds necessary for induction and propagation of colonic contractions.

A recent study (21) has demonstrated that the colon in total colonic inertia did not exhibit electric activity; no PPs or APs were recorded. In a few patients, only the right colon showed sporadic electric waves. The treatment of colonic inertia is problematic and the results of medical and surgical therapies are controversial and mostly unsatisfactory (22-30). Recent studies have shown the potential existence of at least 4 pacemakers in the colon located at the cecal pole, cecocolonic junction, mid-transverse colon (TC) and colosigmoid junction (CSJ) (31). It was demonstrated that the electric waves of the colon start at these sites and that the wave variables differ from one segment of the colon to the other. The electric activity starting at the cecal pole varied in frequency, amplitude and conduction velocity from those evoked at the cecocolonic junction (31). Also the wave variables of the latter were different from those of the descending colon (DC). We suggested that the absence of electric waves in colonic inertia is due to dysfunctioning colonic pacemakers (31).

More recent studies have shown that in colonic inertia patients colonic pacing succeeded in evoking electric activity (32). In view of the aforementioned results we hypothesized that in inertia patients colonic electric waves produced by colonic pacing would initiate colonic motility and effect evacuation. The current communication investigated this hypothesis.

3. MATERIALS AND METHODS

3.1. Subjects

17 patients with constipation due to total colonic inertia were enrolled in the study and divided into two groups: 10 subjects (mean age 45.6 ± 6.3 SD years; range 42-56; 7 women, 3 men) represented the study group, and 7 (mean age 43.7 ± 5.8 SD years; range 40-58; 5 women, 2 men) acted as controls. The mean duration of constipation was 23.2 ± 3.6 SD years (range 18-26); the stool frequency was less than once per week. The patients had followed a high-fiber diet for a long period with no improvement. Defecation was achieved with laxatives, enemas and digitation.

Physical examination including neurologic assessment and laboratory work were unremarkable. Colonoscopy and barium enema studies showed no pathological lesions. Intestinal transit examination revealed total colonic inertia.

Seven healthy volunteers matching the patients in age and gender (mean age 40.9 ± 6.1 SD years; range 38-47; 5 women, 2 men) were also included in the study. They had no gastrointestinal complaint in the past or at the time of enrolment in the study. Mean bowel frequency was 8.6 ± 1.7 / week (range 6-10) which is in accord with that of normal subjects in our laboratory. Physical examination and laboratory work were normal.

All the tested subjects gave an informed consent before being enrolled in the study. The study was approved by our Faculty Review Board and the Ethics Committee.

3.2. Methods

We tested our hypothesis in 2 pacemaker sites: the pacemaker at the mid-TC and the one at the CSJ. The former mediates colonic activity to the left half of the TC and to the DC, while the latter delivers waves to the sigmoid colon (SC) (31). We used 28-gauge cardiac pacing electrodes (Prevail, Medtronic, NC Kerkrade, The Netherlands). One stimulating electrode was hooked to the mucosa overlying the potential site of the pacemaker and 2-3 recording electrodes were applied distally for recording of waves. The stimulating electrode for the left half of the TC and DC was hooked at the mid-TC and 3 recording electrodes were hooked to the colonic mucosa as follows: the first one approximately 5 cm away from the stimulating electrode and the other two with a distance of 8-10 cm between them (Figure 1). The stimulating electrode for the CSJ pacemaker was hooked to the colonic mucosa in the proximal 1-2 cm of the SC, while the two recording electrodes were applied to the SC 5 cm away from the stimulating electrode and with a space of 6-8 cm between each other (Figure 1).

The subjects fasted 8 hours and underwent bowel evacuation by saline enema. The electrodes were introduced into the colon per anum and hooked to the colonic musculature at the above designated sites; this was done through a colonoscope and under videoscopic and fluoroscopic control. 15 minutes were allowed for gut

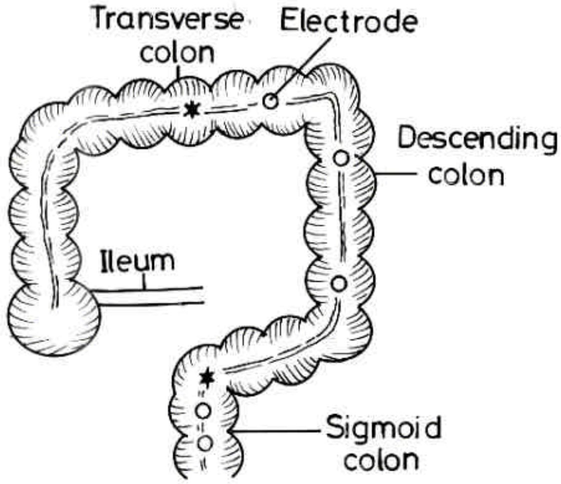

Figure 1. Sites of the electrodes applied to the colon. The stimulating electrodes are marked as stars and the recording ones as rounded spots.

adaptation to the applied electrodes before the start of the test. A 20-minute recording of the basal myoelectric activity was then performed for all the subjects. This was followed in the study patients and the healthy volunteers by a 20-minute recording with electric stimulation of the potential pacemaker sites using an electrical stimulator (model A 310, World Precision Instruments, Sarasota, FL). The stimulator delivered a series of constant electrical current with an amplitude of 5 mA, pulse width of 200 ms and a frequency 15% higher than the already recorded frequency of the basal colonic waves. These parameters had been determined after performing a series of sessions with different pacing parameters. The latency, which is the time lapse from the onset of pacing to the onset of response, was determined. In the control group, recording of the electric activity was done without activation of the pacemaker.

Waves registered from the recording electrodes were amplified using an AC amplifier with a frequency response within ±3dB from 0.016Hz to 1 kHz, and were displayed on an UV recorder at a sensitivity of 1 mV/cm. Simultaneously with colonic pacing the colonic pressure was recorded by means of a 10F tube with multiple side ports and a distal closed end with a metallic clip for fluoroscopic control. With the help of a colonoscope, the tube was introduced endoscopically per anum to lie in the DC. It was connected to a pneumohydraulic capillary infusion system (Arndorfer Medical Specialities, Greendale, WI). The pump delivered saline continually via the capillary tube at a rate of 0.6 ml / min. The transducer outputs were recorded on a rectilinear recorder (RS-3400, Gould Inc, Cincinnati, OH). Occlusion of the recording orifice produced a rising pressure rate greater than 250 cm H_2O/s.

We tested the expulsive effect of colonic pacing on a distended balloon which simulated a stool bolus. A balloon-tipped 6F tube was endoscopically introduced into the DC through the anus. The balloon (London Rubber Industries Ltd, London, UK), 2 cm in diameter, was filled with normal saline in increments of 10 ml. We distended the balloon and then activated the stimulating electrode.

3.3. Colonic pacing at sites away from the pacemaker location

Seven of the colonic inertia patients (study group) and five of the healthy volunteers consented to a study of the effect of colonic pacing at sites away from the potential location of the pacemakers. In the case of the mid-TC pacemaker, the stimulating electrode was hooked approximately to the mid-DC, and in that of the CSJ pacemaker, it was applied to the mid-SC, and the aforementioned tests were repeated.

To ensure reproducibility of the results, the recordings and the measurements were repeated at least twice in the individual subject and the mean value was calculated. The results were analyzed statistically using the Student's t test and values were given as the mean ± standard deviation (SD). Differences assumed significance at $p < 0.05$.

4. RESULTS AND DISCUSSION

We did not encounter adverse side effects during or after performing the tests and all the subjects were evaluated.

4.1. Colonic pacing of the healthy volunteers

Resting electric activity was recorded from the electrodes hooked to the TC, DC and SC. PPs were registered as monophasic waves with a large negative deflection (Figure 2). APs followed, or were superimposed on, the PPs. They appeared as negative deflections and did not follow each PP (Figure 2). The PPs and APs recorded from the 3 electrodes applied to the TC and DC had similar frequency, amplitude and conduction velocity which differed from those registered from the 2 electrodes hooked to the SC. The resting colonic pressure measured 7.3±1.2 cm H_2O (range 6-9). The APs were coupled with increase of the colonic pressure with a mean value of 19.6±3.8 cm H_2O (range 15-23; Figure 3). The PPs were not associated with pressure increase.

Colonic pacing with the aforementioned pacing parameters effected a significant increase in frequency, amplitude and conduction velocity of the waves ($p<0.05$, $p<0.05$, $p<0.05$, respectively; table 1; Figure 2). The latency recorded a mean of 4.3 ± 1.2 s (range 3-7). The rhythm of the electric waves was regular and the wave variables registered from the recording electrodes in the TC and DC were similar although different from those of the SC (Figure 4). When we halted electric pacing, the myoelectric activity returned immediately to the pre-pacing condition; however, in some cases, the effect of pacing waned only after a few more cycles. The colonic pressure during pacing exhibited a significant increase; it recorded, when paced with the aforementioned parameters, a mean value of 58.6 ± 10.2 cm H_2O (range 42-68).

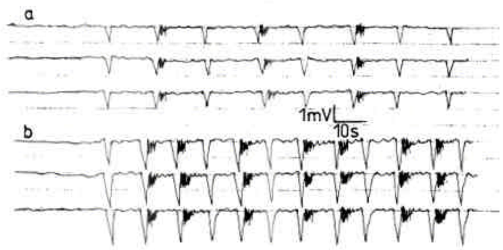

Figure 2. Electric activity of the left half of the transverse and descending colon of a healthy volunteer. The pacesetter potentials occur at a regular rhythm while the action potentials occur randomly. The electric waves were identical from the 3 recording electrodes, a) before colonic pacing and b) after colonic pacing showing increased electric activity.

Figure 3. Electric activity (PPs and APs, upper tracing) and colonic pressure (lower tracing) showing pressure rise with action potentials but not with pacesetter potentials.

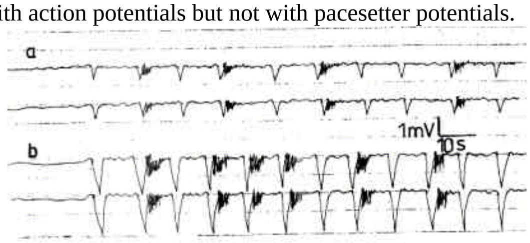

Figure 4. Electric activity of the sigmoid colon of a healthy volunteer showing the pacesetter potentials occurring at a regular rhythm while the action potentials occur randomly. The electric waves were identical from the 2 recording electrodes, a) before colonic pacing and b) after colonic pacing showing increased electric activity.

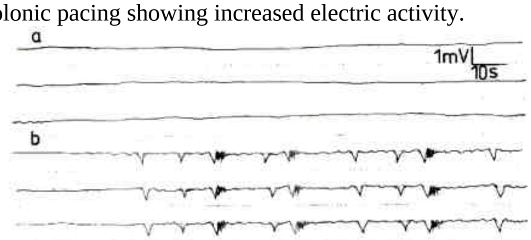

Figure 5. Electric activity of the left colon in a patient with colonic inertia. a) before colonic pacing showing no electric activity, and b) after colonic pacing showing pacesetter and action potentials of irregular rhythm.

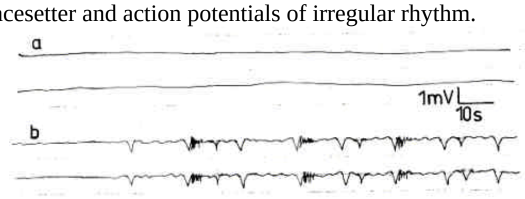

Figure 6. Electric activity of the sigmoid colon in a patient with colonic inertia: a) before colonic pacing showing no electric activity and b) after colonic pacing showing pacesetter and action potentials of irregular rhythm.

The electric activity of the DC and SC before and after pacing with the aforementioned parameters is displayed in tables 1 and 2 and in figures 2 and 4.

4.2. Effect of balloon filling on colonic electric activity in healthy volunteers

The response of the left colon to balloon filling is exhibited in table 3. Small volume colonic balloon distension (10, 20 and 30 ml) did not produce significant change in the basal electric activity or pressure ($p>0.05$; table 3). More increase of the distending volume (40 and 50 ml) increased the wave variables and colonic pressure significantly ($p<0.05$ and $p<0.01$, respectively; table 3), until the balloon was dispelled to the SC at a distending volume of 60 ml of saline.

When we tried colonic pacing with the aforementioned parameters while the colon was distended with a small volume balloon (10, 20 and 30 ml), the ballon was expelled from the left colon to the SC even with only 10 ml distension; the electric wave variables and colonic pressure exhibited a significant increase ($p<0.05$ and $p<0.001$, respectively). Likewise, SC balloon distension with big volumes effected significant colonic pressure elevation and balloon expulsion to the rectum. SC pacing caused balloon expulsion even with small volume colonic distension.

4.3. Colonic pacing in the colonic inertia patients

The study and control groups of patients showed no resting electric activity (Figure 5). On colonic pacing of the study group at the potential sites of pacemakers (mid-TC and CSJ) with the aforementioned parameters, electric waves were recorded after a mean latent period of 10.6 ± 2.2 s (range 7-14). The PP frequency, amplitude and conduction velocity are shown in table 4 (Figure 5). The 3 electrodes applied to the TC and DC showed similar wave variables which differed, however, from those recorded by the SC electrodes (Figure 6). The wave rhythm was irregular and varied during the recording period. The wave variables were significantly lower than those of the healthy volunteers ($p<0.05$).

The resting colonic pressure of inertia patients (study and control) was significantly lower than that of the normal volunteers ($p<0.05$); it recorded a mean value of 3.7 ± 1.1 cm H_2O (range 3-5). Upon colonic pacing of the study group with the aforementioned parameters, the colonic pressure was significantly elevated to a mean of 38.6 ± 6.2 cm H_2O (range 30-44). Balloon distension of the left TC or SC of the study group with the different distending volumes up to 60 ml of saline, effected no significant changes in the colonic pressure nor did it evoke electric activity. When we repeated the test while the left colon or SC were being paced with the above mentioned parameters, the electric activity and colonic pressure showed significant increase and the balloon moved from the mid-TC to the mid or lower DC, while it was dispelled to the rectum upon SC pacing; these movements occurred in all the patients of the study group, even with the 10 ml balloon distension.

Table 1. Frequency, amplitude and conduction velocity of the pacesetter potentials recorded from the descending colon before and after electric pacing of a healthy volunteer[1].

Pacing	**Pacesetter potentials**					
	Frequency (cycle / min)		Amplitude (mV)		Conduction velocity (cm/s)	
	Mean	Range	Mean	Range	Mean	Range
Before	4.2 ± 1.1	3 – 6	1.2 ± 0.3	0.9 – 1.4	4.9 ± 1.2	4.2 – 6.3
After	6.8 ± 1.2[2]	6 – 8	1.9 ± 0.4[2]	1.5 – 2.3	7.5 ± 1.1[2]	6.3 – 8.5

[1] Values were given as the mean ± standard deviation (SD). [2] $p < 0.05$

Table 2. Frequency, amplitude and conduction velocity of the pacesetter potentials recorded from the sigmoid colon before and after electric pacing of a healthy volunteer[1].

Pacing	**Pacesetter potentials**					
	Frequency (cycle / min)		Amplitude (mV)		Conduction velocity (cm/s)	
	Mean	Range	Mean	Range	Mean	Range
Before	5.2 ± 0.7	4 – 6	1.3 ± 0.3	0.9 – 1.5	5.1 ± 0.6	4.3 – 5.8
After	7.2 ± 1.1[2]	6 – 9	2.1 ± 0.7[2]	1.3 – 2.6	7.7 ± 1.2[2]	5.9 – 8.6

[1] Values were given as the mean ± standard deviation, [2] $p < 0.05$

Table 3. Effect of balloon filling on the electric activity of the left colon of a healthy volunteer. [1]

Volume balloon filling (ml)	**Pacesetter potential**							
	Frequency (cycle/min)		**Amplitude (mV)**		**Conduction velocity (cm/s)**		**Pressure (cm H_2O)**	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
0 (basal)	4.2 ± 1.1	3 - 6	1.2 ± 0.3[2]	0.9 - 1.4	4.9 ± 1.2[2]	4.2 - 6.3	7.3 ± 1.2	6 - 9
10	4.3 ± 1.1[2]	3 - 6	1.1 ± 0.3[2]	0.8 - 1.4	4.9 ± 1.2[2]	4.3 - 6.3	7.2 ± 1.2[2]	6 - 9
20	4.2 ± 1.1[2]	3 - 6	1.2 ± 0.3[2]	0.9 - 1.4	5.1 ± 1.2[2]	4.4 - 6.3	7.3 ± 1.2[2]	6 - 9
30	4.3 ± 1.1[2]	3 - 6	1.2 ± 0.3[2]	0.9 - 1.4	4.9 ± 1.2[2]	4.3 - 6.3	7.4 ± 1.2[2]	6 - 10
40	6.5 ± 1.6[3]	5 - 8	1.9 ± 0.8[3]	1.5 - 2.6	7.4 ± 1.7[3]	6.8 - 8.2	14.6 ± 2.7[3]	12 - 18
50	12.8 ± 1.3[4]	11 - 14	3.1 ± 0.9[4]	2.7 - 3.8	8.8 ± 2.1[3]	7.8 - 10.2	26.4 ± 4.3[3]	21 - 32
60			balloon was expelled				58.6 ± 10.2[5]	42 - 68

[1] Values were given as the mean ± standard deviation [2] $p > 0.05$ [3] $p < 0.05$, [4] $p < 0.01$, [5] $p < 0.001$ p - values were compared with the basal value

Table 4. Frequency, amplitude and conduction velocity of the pacesetter potentials of the transverse and descending colon before and after colonic pacing of a patient with colonic inertia [1]

Pacing	**Pacesetter potentials**					
	Frequency (cycle / min)		**Amplitude (mV)**		**Conduction velocity (cm/s)**	
	Mean	Range	Mean	Range	Mean	Range
Before	0	0	0	0	0	0
After	2.6 ± 1.1	2 – 4	0.48 ± 0.02	0.4 – 0.6	Irregular	

[1] Values were given as the mean ± standard deviation

4.4. Change of the pacing location

We studied the effect of colonic pacing when the electrodes were hooked to the colon away from the potential sites of the pacemaker. The stimulating electrodes were transferred from the mid-TC to the DC and from the CSJ to the mid SC. When, in healthy volunteers, colonic pacing with the aforementioned parameters was performed in the DC or SC away from the potential pacemaker sites, we recorded no signicficant changes in the resting colonic pressure or wave variables. Similarly, we registered no colonic wave activity or significant pressure changes upon colonic pacing of the patients with colonic inertia.

4.5. Effective sites of balloon distension and type of colonic movement

In the healthy volunteers, balloon distension at the potential pacemaker sites, e.g. the mid-TC, with a big volume (60 ml) effected balloon expulsion to the SC in "one mass or giant migrating contraction". Likewise, balloon distension of the CSJ with big volume effected balloon expulsion to the rectum in one giant migrating or mass contraction. When we moved the balloon away from the potential pacemaker site and distended it with a big volume (60 ml), the balloon moved in a regular, "step-wise" manner, i.e. it moved for a few cms, then stopped, then moved again, and so on until it reached the SC in case of its location in the DC, or the rectum, when the balloon was placed in the SC. As mentioned, the movement was step-wise in contrast to the mass movement when the balloon was placed at the potential site of a pacemaker.

In colonic inertia, stimulation of the colonic pacemaker while the distended balloon (60 ml) was placed at the potential site of the pacemaker, moved the balloon in one mass to the SC in case of mid-TC pacing, and to the rectum in CSJ pacing. When the balloon was placed distal to the colonic pacemaker, pacemaker stimulation effected balloon movement step-wise but in an irregular fashion; it stopped many times to move again not unless the pacemaker was re-stimulated. In 5 of the 7 patients of the study group, the balloon in the mid-TC succeeded eventually to reach the SC, and in the SC to reach the rectum; however, this occurred after repeated pacemaker stimulation of 2-4 times (mean 3.2 ± 0.9).

The control group of colonic inertia patients in whom the electrodes had been applied to the colon but not activated, showed no electric activity at rest or after application of the electrodes, whether the electrodes were hooked at the pacemaker site or away from it. Also the inserted balloon, without being distended, effected no significant changes in colonic pressure ($p>0.05$).

The aforementioned results were reproducible with no significant difference when the test was repeated in the same subject.

The ultimate treatment of total colonic inertia may be colectomy; however, its results may be disappointing (22-30). The outcome of medical treatment is also unsatisfactory. Therefore the search for alternative therapies for colonic inertia is imperative. In this respect the current study may shed some light on the possible role of an artificial pacemaker in the management of colonic inertia.

The colon of the healthy volunteers exhibited electric activity associated with pressure elevation that was coupled with the occurrence of APs. Colonic pacing at the sites of potential pacemakers effected significant increase of the electric waves and colonic pressure which assumingly indicates an increase of the colonic motor activity. This assumption was verified by distal balloon expulsion on colonic pacing. We used the distended balloon to simulate a stool bolus in the colon. Small volume balloon distension without colonic pacing did not produce significant changes in colonic electric waves or pressure, probably because it did not effect pacemaker stimulation. However, activation of the pacemaker site while it was distended by a small volume balloon, caused significant increase of the colonic electric activity and pressure resulting in expulsion of the balloon.

In colonic inertia, the absence of basal electric waves appears to be responsible for the absence of colonic motility and for the resulting constipation. Previous studies (33-37) have suggested that pacemakers in the gut generate electric waves which presumably initiate the gut motile activity. Accordingly, the absence of colonic electric waves in colonic inertia seems to result from a dysfunction of the colonic pacemakers. The source of the electric waves is claimed to be the interstitial cells of Cajal (ICC) (38-40), which are located at the level of the myenteric plexus and within the circular muscle layer. They are considered to be generators of spontaneous pacemaker activity in the smooth muscle layers of the gut and to be also involved in neurotransmission (38-40).

In colonic iertia, we suggest that the ICC, located at the site of the colonic pacemakers or in the colonic wall, are dysfunctioning. Earlier studies have shown that removal or lesioning of the ICC led to disappearance of the electric waves in the gut (41,42).

4.6. Colonic pacing at the potential sites of pacemakers in inertia patients

Electric waves were produced due probably to activation of the disordered pacemakers. The associated increase of colonic pressure seems to be the result of the initiation of electric activity. The lower wave variables and irregular rhythm obtained after pacing of inertia patients compared to those after pacing of the healthy volunteers appear to be due to the activation of a dysfunctioning pacemaker or disordered ICC. We postulate that the ICC located in the pacemaker sites or in the colonic wall were lesioned so that, when activated, the initiated wave variables could not attain the normal levels. We also observed that the latency, on colonic pacing, was significantly longer in colonic inertia patients than in the healthy volunteers due probably to the delayed response of the dysfunctioning pacemakers.

In colonic inertia patients, big volume balloon distension did not initiate motile activity, due apparently to absent electric activity and failed activation by the distended balloon: the balloon did not move. However, upon colonic pacing, the evoked electric activity with the associated increase of colonic pressure effected balloon movement. Although the wave variables were subnormal and the wave rhythm was irregular, the evoked wave frequency and amplitude were assumingly sufficient to induce colonic motile activity even with the small volume balloon distension.

4.7. A novel theory on the "mass" and "step-wise" movement

The study has shown that colonic pacing is best performed at the potential site of the pacemakers. The type of colonic movement appears to differ according to the site of stimulation: the mass movement occurred with stimulation at the potential pacemaker site while step-wise movement occurred with stimulation away from it; in the latter case the procedure can not be considered as "pacing" but as "electrostimulation". The difference in the balloon movement according to the stimulation site needs to be discussed.

4.8. The pacemaker branching theory

We postulate that, similar to the cardiac pacemaker, the electric waves generated by the colonic pacemakers spread along "pacemaker branches" composed of ICC and nerve fibers of the enteric nervous plexus that extend along the gut wall. Pacemaker stimulation, i.e. "pacing", seems to allow the generated waves to spread along these pacemaker branches producing the giant migrating movement. In the case of electrostimulation away from the site of the pacemaker, we presume that only the ICC at the stimulation site are activated leading to local movements of the balloon, i.e. activating a spread in a step-wise manner and not effecting a single mass movement.

The step-wise movement of the balloon seems to result from a sort of peristaltic activity occurring in the colon similar to that occurring in the small intestine. It is apparently related to the sequential stimulation of ICC located along the gut wall.

In conclusion, colonic pacing led to increase of the electric activity of the colon in healthy volunteers. It evoked electric waves in the colonic inertia patients and succeeded in effecting balloon expulsion. Pacing at the pacemaker locations produced colonic mass contraction, while away from the pacemaker sites a step-wise movement. We postulate that the pacemaker generates electric waves which spread along pacemaker branches that are composed of ICC and nerve fibers of the enteric nerve plexus. The electric waves evoked by pacemaker stimulation appear to spread along these branches and effect colonic mass contraction. Ex-pacemaker stimulation presumably leads to local ICC activation and segmental colonic contraction in a sequential step-wise manner. Colonic pacing in the treatment of constipation due to colonic inertia needs to be further investigated in humans as a therapeutic method of intractable cases.

5. ACKNOWLEDGMENT

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Send correspondence to: Ahmed Shafik, MD, PhD, 2 Talaat Harb Street, Cairo, Egypt, Tel/Fax: +20-2-749 8851, E-mail: ashafik@ahmedshafik.org, URL: www.ahmedshafik.org