Kafkas Univ Vet Fak Derg
15 (2): 315-322, 2009
DOI:10.9775/kvfd.2009.037-D

REVIEW

Detailed Characteristics of the Migrating Motor Complex in Man and Animals

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Yayın Kodu (Article Code): 2009/037-D

Summary

During the interdigestive state occurring in monogastric species, the stomach and small intestine are almost empty. The meal consumed during the foregoing period undergoes the digestive and transport processes. Notwithstanding, the relatively small amounts of indigestible food remnants, cellular debris, bacteria and possibly the small portions of ingested liquids and solid foods may remain in the gastrointestinal lumen. The secretion of the digestive juices is not inhibited completely during the fasting state and the presence of the digestive juices in the gastrointestinal lumen appears to be one of the main reasons to maintain the transport of the luminal content during this period. There is no need to retain an uninterrupted mixing of gastrointestinal flow of digesta as it occurs during the postprandial period. Thus, the character of motor activity present in non-fed humans and monogastric animals adapts to the actual conditions and the interdigestive motility exhibits the cyclical character. Therefore, it was defined as cyclic motor activity and these cycles are regarded as the migrating motor complexes (MMCs). The MMC comprises four phases exhibiting the exponential intensity of contractions: phase I was defined as the weakest or with no contractions; during usually the longest phase II, divided sometimes into phase IIa and IIb, the increased frequency and amplitude of contractions are noticed; in the course of phase III, the strongest contractions occur at the maximal frequency; during phase IV, not always observed, the irregular submaximal contractions, similar to those during phase II can be recorded. There are quite precise criteria for MMC identification and it is possible to distinguish normal and abnormal MMCs. This fasting pattern occurring in most mammals and birds, is organized during the fetal life and in some species, like ruminants and other herbivores, is not abolished by feeding. The manometric technique still appears to be the gold standard method in man and promising in animals at least for the gastric and small-intestinal MMC registration to allow more detailed analysis of the interdigestive motility than the other minimally invasive methods used for clinical purposes.

Keywords: *Interdigestive motility, Man, Animals, Identification, Methodology, Coordination*

İnsanda ve Hayvanlarda Göç Edici Motor Kompleksin Özellikleri

Özet

Interdigestive dönemde tek mideli türlerde mide ve ince barsaklar tamamen boştur. Başlangıç periyodunda tüketilen gıdalar sindirim ve transport işlemine uğrarlar. Bununla birlikte nispeten küçük miktarlarda sindirilemeyen gıda kalıntıları, hücresel döküntüler, bakteri ve muhtemelen çok az miktarda sindirilemeyen sıvı ve katı gıdalar gastrointestinal lümende kalır. Sindirim sıvılarının salgılanması açlık safhasında tamamen inhibe edilmez ve gastrointestinal lümende sindirim sıvılarının kalması bu safhada lüminal içeriğin taşınmasının ana sebeplerindendir. Yemek sonrasında olduğu gibi gastrointestinal gıda karışımının aralıksız olmasına da gerek yoktur. Dolayısıyla gıda almayan insane ve tek mideli hayvanlarda mevcut motor aktivitenin özelliği gerçek durumlara uyum sağlar ve interdigestive motilite siklik özelliktedir. Bu nedenle siklik motor aktivite olarak tanımlanır ve bu sikluslar göç eden motor kompleksler (MMCs) olarak kabul edilirler. MMC gittikçe artan kontraksiyon yağunluğu gösteren dört safhayı kapsamaktadır; genelde en uzun safha olan bazende faz IIa ve IIb olarakta ayrılan faz II döneminde, kontraksiyon şiddeti ve sıklığı belirlenmektedir; faz III sırasında en güçlü kontraksiyonlar maksimum sıklıkta belirlenir; her zaman belirlenemeyen faz IV döneminde faz II dönemine benzer düzensiz azami olmayan kasılmalar kaydedilir. MMC tanımlanmasında kesin kriterler mevcuttur ve bu normal ve anormal MMCs durumların ayırt edilmesini mümkün kılar. Birçok memeli ve kuşlarda gerçekleşen bu açlık dönemleri fötal yaşamda organize edilmekte ve ruminat ve diğer ot oburlar gibi bazı türlerde beslemeyle ortadan kalkmamaktadır. Monometrik teknikler hala insan ve hayvanlarda en azından gastric ve intestinal MMC kaydedilmesinde altın standart metot olarak görünerek interdigestive motilitenin detaylı analizini klinik amaçla kullanılan diğer minimal invaziv metotlardan daha detaylı nalizlerine imkan vermektedir.

Anahtar sözcükler: ***İnterdigestive motilite, İnsan, Hayvan, İdentifikasyon, Metodoloji, Koordinasyon***

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BACKGROUND

In man and other species of mammals and birds, the majority of previously ingested foods is absent in the stomach and small bowel during the interdigestive period, also called the fasting state. The secretion of the small amounts of gastric, pancreatic, and intestinal juices and bile still occurs. Since the digestive and absorptive processes are preserved there is also need to mix and transport the luminal content and to sustain the motor function over this period. The movement of the gastrointestinal wall facilitates the intramural blood and lymph flow, ensures the smooth muscle training and affects mixing, digestion, absorption and probably the release of regulatory substances from the endocrine mucosal cells [1]. This allows to maintain the labile equilibrium between the secretory and absorptive processes in the fasting state what in turn contributes to preserve physiological conditions in the gut. The existence of some active contractions prevents the bacterial overgrowth especially in the proximal small bowel. During the interdigestive state these functions occur in the cyclic (interrupted) fashion, since there is no need to maintain the continuous motor activity because the volume of the intestinal content is much smaller than during the digestive state and periodic transport of the digesta is sufficient. Therefore, the cyclic character of the interdigestive motility including the alternating quiescent and active motility periods seems reasonable. Thus, it was proposed to call these cycles the migrating motor complex (MMC) or the interdigestive MMC [2]. The cyclic character of the MMC enables an undisturbed transport of the intestinal content when necessary since it is well coordinated. The presence of the quiescent period in the MMC cycle facilitates the interdigestive secretions. Its active phases ensure the physical smooth muscle training and exhibit some trophic aspects. The aim of this elaboration was to present the actual view upon the interdigestive motility of the stomach and small intestine with special emphasis on the MMC recording methods, identification, characteristics, and coordination in man and some animal species.

THE MIGRATING MOTOR COMPLEX METHODOLOGY AND IDENTIFICATION

The MMC cycle present in most mammals and birds, arrives in early fetal period and occurs during the whole life [3-6]. Species differences regarding the MMC are rather quantitative than qualitative and, for example, species differences of the mammalian small intestine are smaller than those found at the proximal and distal ends of the digestive tract [6,7]. However, there are some exceptions. In monogastrics, including man, dog, and rat, the MMC cycle is disrupted by feeding what is not the case in ruminants; pigs represent the transient model in this scope [6,8-10]. Rather no MMC is present in cats, the intense spike bursts series arrive instead [11]. The MMC cycles occur in the stomach and the whole intestine and cyclic motor activity also arrives in the lower esophageal sphincter, the gallbladder, the sphincter of Oddi, and may pass from the ileum till the colon through the ileocolonic junction. Thus, the MMC present in one gastrointestinal segment is well correlated with that in the adjacent regions [6,12-14].

The myoelectrical MMC recordings, classic studies

The description of the MMC pattern was first published by Szurszewski [2] and six years later Code and Marlett [15] proposed the detailed criteria for identification of the MMC and its phases in the dog considering the myoelectrical recordings. Accordingly, the MMC was regarded as the four-phase complex arriving cyclically in fasted animals, beginning with phase I and terminating with phase III or IV *(Fig. 1)*. In the stomach and small bowel, phase I of the MMC was characterized by the relative absence of action potentials as compared to other phases. The first three min. recording period, during which at least 10% of the slow waves were occupied with the spike bursts, was identified as phase II onset unless it was followed by more than six minute recording period during which the spike bursts were less frequent. Phase III of the MMC was characterized by the continuous series of the intense spike bursts, with abrupt onset, superimposed on every slow wave. Phase IV of the MMC was described by rapid decrease in frequency and intensity of the spike bursts. During at least three min. recording period the incidence of the spike bursts related to slow waves was less than 10% and this low spike burst frequency continued for more than six minutes. The duration of the whole MMC cycle and its phases was measured in various animal species. Although Stanciu and Bennett [16] were first to record the MMC in man, Fleckenstein and his collaborators [17,18] presented the elegant results of performed myo-

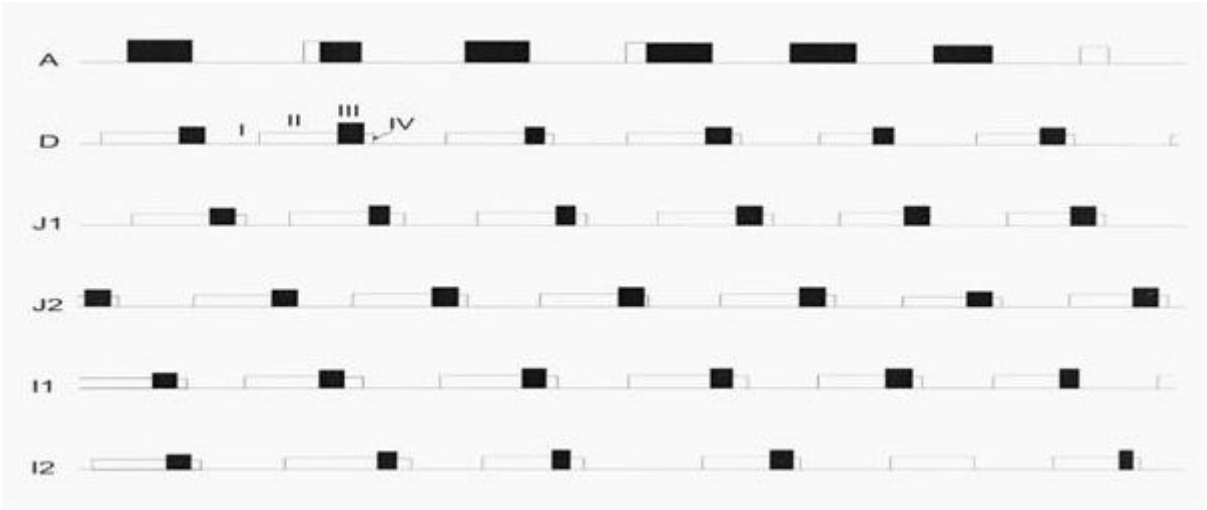

Fig 1. Scheme of the 10-hour recording of the interdigestive motility of pyloric antrum, duodenum, and jejunum in fasted dog. Cycles of the migrating motor complex (MMC) originate usually from antrum and terminate most often in terminal ileum. Phase IV not always present. Explanations: **I-IV -** MMC phases, **A -** pyloric antrum, **D -** mid duodenum, **J1 -** proximal jejunum, **J2 -** distal jejunum, **I1 -** mid ileum, **I2 -** distal ileum

Şekil 1. Aç köpeklerde pilorik antrum, duedenum ve jejenumda interdigestive motilitenin 10 saatlık kayıt şeması. İlerleyicic motor kompleksin siklusları (MMC) genelde antrumda başlar ve terminal ileumda sonlanır. Faz IV her zaman mevcut değil. Açıklamalar: **I-IV -** MMC fazları, **A -** pyloric antrum, **D -** orta duodenum, **J1 -**proximal jejunum, **J2 -** distal jejunum, **I1 -** orta ileum, **I2 -** distal ileum

electrical registration of the MMC using not fixed suction electrodes, mounted in the tube inserted into the gastrointestinal tract. Fleckenstein et al.[18] characterized the MMC as the three-phasic cycle with total duration 145-172 min that was measured between the onsets of the phases III of two consecutive MMC cycles at the same recording site. Phase I of the MMC, occurring without spiking activity, lasted 20-90 min, phase II of the MMC with randomly arriving spike bursts lasted 35-135 min and phase III of the MMC (regular spiking activity) lasted 145-680 sec. The average migration velocity of phase III observed in the duodenum was 12 cm/min. In spite of several successful MMC recordings with the electromyographic method including either electromanometry or serosal electrode implantation [19,20], during the next decades other methods for the MMC registration in humans predominated because the suction electrode method was harmful to the gastrointestinal mucosa. In the pig' classic study [10] the MMC consisted of three phases and lasted 75-80 min. Phase I was described as the quiescence 10-20 min period. It was followed by phase II of the irregularly arriving short spike bursts engaging about 30% of the slow waves with the duration 50-55 min. Phase III of the MMC was defined as the large spike bursts occurring with the frequency of the slow waves and lasting about 5 min. In 24-h fasted rats, the duration of the MMC cycle lasted about 17 min, i.e. the MMC arrived 3-4 times per hour [21]. Three phases can also be distinguished. In the jejunum, phase I, the quiescent period, lasted 6.1±2.4 min; phase II representing the irregular spiking activity occupying about 30% of the slow waves, lasted 6.6±1.3 min; phase III during which the regular spiking activity of the greatest duration (about 1.5 sec) and amplitude (about 150 μV) was observed, lasted 4.3±0.4 min. Not all phases III travelled over the whole small intestine. In rabbits the MMC pattern occurred in both fasted and fed state [22]. The MMC cycle in fed rabbits lasted 118-160 min while in 24-h fasted rabbits lasted 107-157 min. Phase I defined as the quiescent period lasted only 5-10 min. Phase II was the longest, irregular spiking activity occupying 70-80% of the MMC cycle duration. Phase III, the regular spiking activity lasted 7-15 min and in 65.5±7.3% propagated from the jejunum to the ileum. This phase was absent in the duodenum. Phase IV was described as the spike bursts of decreasing amplitude from the regular phase to a quiescent period and lasted for up to 20 min (0-20 min). In non-fasted sheep [23], the jejunal MMC cycle lasted 88.4±16.2 min while the duration of phases I - III (the inactivity, the irregular and regular activities) was 42.0±15.1, 40.1±4.8 and 6.2±1.2 min, respectively. The propagation velocity of phase III

averaged for 17.8±5.7 cm/min. In this species the MMC started most often from the duodenum [24]. In the last decades most of these data were confirmed in man, dog, pig, rat, rabbit, guinea pig and chicken [25-31]. The MMC cycle can also be recorded in other animal species and in the last two decades mouse joined the list of the animal species used as the model for human beings. In mice the duration of the MMC was reported to be approximately twice shorter than in the rat [32,33].

The mechanical recordings, classic studies

One of the first MMC mechanical recording studies was performed in man by Vantrappen et al.[34] who used the typical manometric technique. Three criteria were applied to identify the MMC: presence of an uninterrupted series of pressure waves at the frequency of about 12 cycles per minute at the level of the angle of Treitz ligament, i.e. the activity front (phase III of the MMC); aboral progression of phase III; arrival of the period of absolute quiescence after phase III of the MMC. The MMC cycle duration was 113±47 min. Phase I was considered as nearly complete absence of the pressure waves. Phase II was characterized by the irregular pressure waves. The activity front was described as an abrupt arrival of the rhythmic contractions sometimes preceded by a short quiescent period. Its duration in the duodenum and in proximal jejunum was 5.0±0.6 and 5.5±0.4 min., respectively and propagation velocity in the duodeno-jejunum 7.7±1.1 cm/min. Soon after, Dent et al.[35], identifying the MMC pattern, classified the duodenal phase I of the MMC as quiescence, phase II as the occurrence of irregular contractions at the frequency below 10/min and phase III as the regular contractions at the frequency of 10-14/ min and duration ≥2 min. However, in the stomach they distinguished phase I also as the quiescent period, phase IIa as the irregular contractions generally low in amplitude, phase 2b as more regular contractions with the frequency ranging 0.5-2.2/min and lasting 2 min or longer and phase III of the MMC as the regular contractions at a rate of about 3 cycles per minute (cpm) [35].

Thus, the manometric techniques gradually became the most common for the recording of the inter-digestive motility in man. The MMC parameters in man have been proposed [36,37]. However, there is lack of the uniform precise criteria for MMC identification. The definitions of the MMC cycle and its phases are roughly similar but still some differences occur. Usually phase IV is not recognized or included into phase III of the MMC. Sometimes the MMC and its phases are only briefly described or remain undefined [38-40]. The manometric technique is also applied in the dog, for the interdigestive motility study, although, with some modifications [41-43].

Other methods applicable for MMC recording

There is variety of the in vivo methods assessing the gastrointestinal motility [44,45]. Unfortunately, only few of them can be employed for the monitoring of the interdigestive motility. They comprise the manometric recordings in man and animals, mechanical recordings with the use of pressure transducers including the miniature ultrasonic transducers [46], applied principally in animals, as well as the electromyographic techniques also used preferably in animals. These methods require longer multichannel motor or myoelectrical recording and usually the expensive machinery. The techniques used for the estimation of gastric emptying and intestinal transit as well as the electro-gastrography are not helpful. Other techniques including the application of radiotelemetric capsule [47,48] are not in common use. Radiotelemetry is currently combined with the electromyography [49,50]. The implanted telemetry transmitter in the abdominal wall can transmit the signal from the serosal electrodes to the receiver and to be archived by a computer. Impedancometry, another new technique, applied recently in pigs for the recording of the duodenal interdigestive motility [51,52] might be considered as promising perspective in the systematically enlarging bunch of the available methods in this area. The development of the per-cutaneous implantation of the gastric electrodes [53] can facilitate the recording of the MMC in the stomach and compete with electrogastrography [54]. The methods registering any changes in the magnetic capsule [55] represent the further promising perspective, especially for clinical investigations. Despite of the variety of methods, new less invasive techniques are keenly awaited.

CHARACTERISTICS OF THE MIGRATING MOTOR COMPLEX

The MMC cycles exhibit the considerable variability in the cycle and phase duration, arrival and disappearance of phase III and also, to some extent, in the amplitude and frequency of the spike bursts or contractions during the irregular

phases. Arrival of phase I of the MMC can be understood rather as the existence of the obstacle for the induction of contractions than as the result of active initiation since it is believed that the refraction occurs during this MMC phase [56]. When no contraction is present it can be assumed that the absolute refractory period arrived. When the increasing incidence of contractions is recorded during phase I or at the beginning of phase II of the MMC, it suggests the presence of the relative refractory period. There is relationship between duration of phase I and phase II [57]. Furthermore, it was suggested that phase I may be controlled by phase III activity at distal segments of the gut [57] but the precise mechanisms for phase I generation are unknown. Phase II of the MMC is most often the longest phase of the cycle. Therefore, as stated above, Dent et al.[35] suggested its division in the human stomach into phase IIa and IIb. It can also be divided in the gut what was already demonstrated in sheep [58]. The greater incidence of the spike bursts than during phase IIa, usually above 20 % of the slow waves occupied by the spike bursts with the duration ≥2 min, was classified as the beginning of phase IIb [59]. The duration of phase IIa was roughly similar to the duration of phase IIb [35,59]. Phase II of the MMC represents the basic activity and it was suggested that its length might be determined by the occurrence of phase III of the MMC [57]. The character of phase II was described most often as irregular incidence of the spike bursts or contractions. However, its nature was studied more precisely and it was revealed that phase IIb is interrupted with less active periods, spike bursts seem to be less dispersed than in the postprandial period when propagated clusters of spike bursts were more frequently observed [60,61]. Similar observations were performed in sheep [62]. It seems likely that phase II can be less propulsive than the fed pattern, but generally phase II of the MMC and the fed pattern are hardly distinguishable.

Phase III is believed to be the most characteristic of the phases forming the MMC cycle. It is probably the only phase migrating down along the gastrointestinal tract [57]. Within phase III single contractions or spike bursts are propagated while in the last part of this phase the retropropagated activity was described in the duodenum [63]. An interesting observation was reported by Zenilman et al.[64]. The authors described in rats only partial disruption of the MMC cycle after feeding using time series analysis with fast Fourier transforms. It may suggest that phase III of the MMC can be generated also after feeding. Thus, the MMC cycle duration can be determined by gastric and/or duodenal origin of phase III [65].

COORDINATION OF GASTROINTESTINAL FUNCTIONS DURING THE INTERDIGESTIVE STATE

Coordination of the gastrointestinal motility within the MMC

Three basic levels of coordination of the gastrointestinal motility in the interdigestive state (MMC) can be distinguished. First comprises the relationship between the slow waves and spike bursts. The frequency of the slow waves in the given gastrointestinal region somehow determines the frequency of the spike bursts and contractions, especially during phase III of the MMC when the incidence of the spike bursts and contractions is the highest. The slow wave frequency during various phases of the MMC cycle is variable [66-68]. Nevertheless, it appears that in the murine small bowel the MMC is not coupled with the slow waves [33]. The intestinal intrasegmental coordination represents the second level of coordination of the MMC cycles. This means that within the given gastrointestinal shorter or longer segment the single spike bursts and contractions (or their lack) behave in well-organized fashion [69,70]. The mode of migration of the spike bursts, especially during phase III of the MMC, for example within the duodenum is the best illustration of this physiological event. The third level comprises the intersegmental coordination of the MMC in the gut. This can be outlined with the mutual interrelationships among the adjacent regions including lower esophageal sphincter, stomach, pylorus, duodenal bulb, the duodenum, the jejunum, the ileum and the ileo-cecal sphincter. The myoelectric and motor cooperation between these regions allows for thornless migration of phase III of the MMC in organized fashion. Migration of phase III from the stomach towards the duodenum is undisturbed since the pylorus is almost completely open during interdigestive antral contractions [71]. Phase III migrates often to the terminal ileum and the luminal content is transported into the colon [72]. Several physiological studies in this area can further document the existence of precise coordination of motility during the interdigestive state [12,65,66,73-79]. Esophageal motor function is

correlated with the onset of phase III of the MMC that may start from the lower esophageal sphincter and travel through the entire stomach and pylorus to the small intestine. Migration of the MMC downward requires good motility coordination and continuous support from other mechanisms including the sustained activity of the enteric nervous system, changes in motilin release, and coordination with the digestive secretory processes as it is pointed below. Furthermore, there is also coordination between distant gastro-intestinal regions comprising the pancreas. Motor activity of the terminal ileum is well coordinated with the ileocecal sphincter and large intestine not only during phase III of the MMC, but also during other active periods of the interdigestive state. The application of some surgical procedures confirmed these findings and stated that the gastrointestinal wall continuity is responsible for this coordination [76,80,81].

Coordination of the MMC with other gastrointestinal functions

Soon after the MMC concept was established it was found that the duodenal pH is increased around the onset of the duodenal phase III [82]. Thus, in 1977-1980 the couple of reports appeared presenting the studies upon the fluctuations in gastric, pancreatic and biliary secretions in man and dog in accordance with the MMC [83-88]. These events were called the secretory component of the MMC. The authors found the relatively small but significant increases in gastric acid and pepsin secretion from the stomach and bicarbonate, amylase and bile inflow into the duodenum as compared with the digestive period. These results were confirmed in the later studies in man and animals [89-92]. The increase in gastric and biliary secretions occurred in the second half of the duodenal phase II and the increase in pancreatic secretion rather at the end of phase II of the duodenal interdigestive cycle. The cyclical intensity of the interdigestive motor activity must ensure the optimal transit of chyme in the small bowel and facilitate the presence of optimal absorptive processes [93,94]. Phase III of the MMC is the major driving force to transport the chyme aborally, toward the hindgut. As it can be expected, changes in motility and secretion observed in the course of the MMC cycle alter the absorption dynamics in the gut. The villous motility alterations might participate in these effects. Thus, the interdigestive motility may contribute significantly to the balance between absorptive and secretory function in the small intestine [95].

CONCLUDING REMARKS

Considering above description of the MMC it can be inferred that the interdigestive cycle is quite well characterized and this characterization appears to be detailed enough to recognize the normal pattern in man and some animal species including dog, pig, rat, rabbit and even the mouse. This should be sufficient to recognize the MMC abnormalities in these species. Systematic studies on these abnormalities may facilitate understanding of pathogenesis of diseases with accompanied disturbances of digesta transport.

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