In the fasting state the motility of the stomach and small intestine is characterized by a cyclic pattern of contractions, the migrating motor complex (MMC). The MMC was first described in 1969 by Szurszewski (26), who recorded intestinal migrating myoelectrical activity in dogs and observed changes in this activity according to a cyclic pattern. His findings were confirmed in humans by Vantrappen et al. in 1977 (29). The MMC has an important role as “intestinal housekeeper” (4), and especially phase III contributes importantly to interdigestive flow (11). The MMC functions as a barrier against the migration of bacteria, viruses, and parasites from the lumen of the small intestine into the veins of the portal system (6, 9, 21).

The importance of gastric or duodenal origin of phase III activity is a matter of debate. The MMC has been observed to have three phases: phase I of motor quiescence, phase II of interdigestive flow, and phase III of migrating motor complex (MMC). The MMC is divided into three phases: phase I of motor quiescence, phase II of interdigestive flow, and phase III of migrating motor complex (MMC).

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ized water at a constant rate of 0.3 ml/min. Pressures were measured by external transducers (DPT-200, Medisize, Hillegom, The Netherlands) and stored in a digital portable data logger (Medical Measurement Systems, Enschede, The Netherlands) using a sample frequency of 4 Hz. The catheter was fixed to the nose after confirmation of the correct position by the recorded pressures. The correct position of the catheter in the antrum and duodenum was continuously monitored by measurement of the transmucosal potential difference, which was recorded at the most distal antral side hole and the most proximal duodenal side hole (5 cm apart). A gastroduodenal transmucosal potential difference gradient of at least 15 mV was maintained throughout the study. A cutaneous electrode was attached to the chest below the collar bone to serve as a reference electrode.

Data analyses. Manometric recordings were analyzed semi-automatically. The distal antral recording site and the third duodenal recording site (20 cm distal to the pylorus) were used to visually identify phases I, II, and III. Phase I was defined as a period with no pressure waves starting just after the end of phase III. Phase II in the duodenum or antrum started at the first appearance of at least three pressure waves in a 10-min interval. Phase II was characterized by irregular pressure waves occurring at a rate of <2 waves/min in the antrum and <10 waves/min in the duodenum. Phase III in the antrum was defined as rhythmic contractile activity, with a frequency of 2.5–3 pressure waves/min for at least 2 min in temporal relationship with a duodenal phase III and followed by motor quiescence (phase I). Phase III in the duodenum was defined as rhythmic pressure waves with a frequency of 10–12 pressure waves/min propagated over at least two recording sites and followed by phase I. Phase III activity starting in the distal duodenal (third or fourth) recording site and followed by phase I was also defined as a phase III, although distal propagation could not be observed (9, 25). The site of origin of each phase III was noted. A phase III that was recorded in the antrum, which could also have been started in the lower esophageal sphincter or proximal stomach (7, 9), was defined as a phase III of antral origin and will be indicated with quotation marks. Figure 1 shows a manometric recording of a MMC with a phase III of “antral” origin (Fig. 1A) and of duodenal origin (Fig. 1B), respectively. Total cycle duration in the duodenum was calculated from the end of phase III to the end of the next phase III.

Pressure wave amplitude and frequency were automatically calculated for phases II and III within each MMC period separately (23). Duodenal propagation velocity of phase III was calculated by measuring the time interval between the onset of phase III at the second and fourth duodenal side hole (10 and 30 cm distal to the pylorus, respectively). All manometric data given represent the observation at the duodenal recording site, unless otherwise stated.

Statistical analysis. All variables followed a normal distribution and are expressed as means ± SE unless otherwise indicated. The presented means are unweighted means, i.e., means of all subjects after first calculating the mean within each subject separately. The corresponding SEs were calculated as square root of mean squares (residue) divided by number of subjects, from the ANOVA model. The MMC characteristics; MMC cycle duration; duration of phases I, II, and III; pressure wave incidence; mean amplitude; and propagation velocity were examined by using the ANOVA model, both before and after discriminating for “antral” or duodenal phase III origin effects. The homogeneity of variance for each variable, after dividing into “antral” and duodenal phase III origin effects, was tested and appeared equal. Within-subject and between-subject effects were given by the ANOVA model. For the MMC cycle duration, the corresponding variance components between and within individuals (s^2_M and s^2_w, respectively) were used to calculate the variance between individuals as a percentage of the total variance (Vr): s^2_M/(s^2_M + s^2_w) (8). To explain the importance of the factor preceding phase III origin in the total variance, the sum of squares of the factor preceding phase III origin was calculated as a percentage of the total sum of squares in the ANOVA model (proportion explained variance). The effect of unfamiliarity with gastrointestinal catheter studies (stress factor) on MMC cycle duration was examined using the ANOVA model. Multiple regression was used to test the association between the duration of phase III and its propagation velocity. Statistical significance was defined as two-tailed P < 0.05.

RESULTS

The mean recording time in the subjects was 448 ± 50 (SD) min, with a mean of 2.8 ± 1.2 (SD) MMC cycles in each subject. In all subjects, except one who showed only one complete MMC, at least two complete MMC cycles were observed. The total number of MMC cycles recorded was 53. There was no difference between the four catheter-inexperienced volunteers and the others who had participated in previous experiments. None of the subjects experienced vomiting or feelings of nausea after catheter intubation. The first recorded phase III appeared at 108.5 ± 14.9 min after intubation and was of “antral” origin in 14 of the 19 subjects.
The duration of phase III was significantly different following a phase III of duodenal origin (significantly longer compared with the MMC cycle duration following a phase III of "antral" origin was also significantly different between MMC cycles following a phase III of "antral" origin and those originating from a duodenal or "antral" origin. The MMC cycle duration shown as a solid line. In Fig. 2, we could clearly distinguish between MMC cycles for 76%, and phase III for 5%. In total, 72 phase III cycles were observed with 35 (49%) of "antral" origin and 37 (51%) of duodenal origin. Seventy-seven percent of the total variance in MMC cycle duration was explained by the within-subject variance ($V_b = 23$). The duration of phase III was significantly different between subjects ($P < 0.01$). Other MMC characteristics with a significant between-subject difference were phase III pressure wave amplitude in duodenum and antrum ($P < 0.01$) and phase III propagation velocity in the duodenum ($P < 0.01$).

The large variability in MMC cycle duration is also visible in Fig. 2, showing for each subject the cycle duration of all MMC cycles separately, with the overall mean MMC cycle duration shown as a solid line. In Fig. 2, we could clearly distinguish between MMC cycles following a phase III of "antral" origin and those following a phase III of duodenal origin. The MMC cycle duration following a phase III of "antral" origin was significantly longer compared with the MMC cycle duration following a phase III of duodenal origin ($P < 0.001$; Table 2). When the factor preceding phase III was of "antral" origin (76.0 min), the duration of phase I was significantly longer when the preceding phase III was of "antral" origin (76.0 $\pm$ 5.3 min) than when of duodenal origin (32.5 $\pm$ 5.2 min, $P < 0.001$). The mean amplitude of antral pressure waves during phase II was significantly greater when this phase II resulted in a phase III of "antral" origin compared to phase II resulting in a phase III of duodenal origin ($P < 0.01$). The amplitude of duodenal pressure waves during phase III was not significantly different between a duodenal or "antral" origin of this phase III.

Besides the discrimination in MMC characteristics following a phase III of "antral" or duodenal origin, we also observed that phase III duration in the duodenum was dependent on the place of origin of this phase III. Phase III was significantly longer when it started in the "antrum" and propagated into the duodenum than when phase III started in the duodenum ($P < 0.001$, Table 3). Phase III propagation velocity, pressure wave incidence, and amplitude in the duodenum were not significantly different between the phase III of different origin, although the propagation velocity and amplitude showed large variations between subjects ($P < 0.01$). The propagation velocity and duration of phase III in the duodenum were not associated when between-

### Table 1. Parameters of fasting antroduodenal motility in healthy subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Means ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC cycle duration, min</td>
<td>117.3 ± 13.9</td>
</tr>
<tr>
<td>Phase I, min</td>
<td>22.6 ± 4.0</td>
</tr>
<tr>
<td>Phase II, min</td>
<td>91.1 ± 12.4</td>
</tr>
<tr>
<td>Phase III, min</td>
<td>6.4 ± 0.4*</td>
</tr>
<tr>
<td>Antral/duodenal phase III number</td>
<td>35/37</td>
</tr>
<tr>
<td>Propagation velocity, cm/min</td>
<td>12.5 ± 1.3*</td>
</tr>
<tr>
<td>Phase III pressure wave incidence, pressure waves/min</td>
<td>11.3 ± 0.2</td>
</tr>
<tr>
<td>Phase III pressure wave amplitude, kPa</td>
<td>4.2 ± 0.2*</td>
</tr>
</tbody>
</table>

Values are shown for duodenum; $n = 19$ subjects. MMC, migrating motor complex. Propagation velocity is propagation of phase III from 10 to 30 cm distal to pylorus. *Significantly different between subjects, $P < 0.01$.

### Table 2. Parameters of fasting antroduodenal motility following a phase III of antral or duodenal origin

<table>
<thead>
<tr>
<th>MMC Characteristics</th>
<th>After Phase III of Antral Origin</th>
<th>After Phase III of Duodenal Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC cycle, min</td>
<td>156.1 ± 11.0</td>
<td>80.5 ± 10.7*</td>
</tr>
<tr>
<td>Phase I, min</td>
<td>33.1 ± 3.5</td>
<td>13.3 ± 3.5†</td>
</tr>
<tr>
<td>Phase II, min</td>
<td>116.0 ± 11.1</td>
<td>60.5 ± 10.8†</td>
</tr>
<tr>
<td>Phase III, min</td>
<td>6.0 ± 0.4</td>
<td>6.6 ± 0.4†</td>
</tr>
</tbody>
</table>

Values are shown for duodenum as means ± SE; $n = 19$ subjects. *Significantly different between different origin of phase III ($P < 0.001$ for MMC cycle duration, phase I, and phase II; $P < 0.05$ for phase III). †Significantly different between subjects ($P < 0.01$ for phase I; $P < 0.05$ for phase II and III).

### Table 3. Characteristics of phase III when discriminating for origin of ongoing phase III

<table>
<thead>
<tr>
<th>Phase III Characteristics</th>
<th>Phase III Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, min</td>
<td>7.6 ± 0.4</td>
</tr>
<tr>
<td>Propagation velocity, cm/min</td>
<td>12.5 ± 1.3</td>
</tr>
<tr>
<td>Pressure wave incidence, pressure waves/min</td>
<td>11.4 ± 0.2</td>
</tr>
<tr>
<td>Pressure wave amplitude, kPa</td>
<td>4.1 ± 0.2</td>
</tr>
</tbody>
</table>

Values are shown for duodenum as means ± SE; $n = 19$ subjects. Propagation velocity of phase III from 10 to 30 cm distal to pylorus. *Significantly different between phase III of different origin ($P < 0.001$). †Significantly different between subjects ($P < 0.01$).
subject and phase III origin effects were included in the equation.

**DISCUSSION**

The MMC in humans is subject to large variations in its characteristics, both between individuals and within an individual. The reason for this wide variation is unknown. Our results contribute to a better understanding of this variation. In this study we show that MMC characteristics depend on the origin of phase III of the MMC. After a phase III of "antral" origin, the MMC cycle duration and duration of phases I and II are longer than following a phase III of duodenal origin. The duration of phase III in the duodenum depends on the place where this phase III starts, with a longer duration when phase III starts in "antrum" compared with when it starts in the duodenum. Therefore, the variability in origin of phase III, with about 50% of the phase III cycles starting in the "antrum" and 50% starting in the duodenum, explains part of the within-subject variance in MMC characteristics.

The mean overall data on MMC cycle duration in our study correspond with previous stationary manometry studies on gastroduodenal MMC characteristics in humans, reporting a mean MMC cycle duration ranging from 105 to 114 min (9, 16, 22, 25). All these studies report large variations in MMC cycle duration, which Husebye et al. (8) attributed 90% to within-subject variance. In our study this within-subject variance contributed 77% to the total variance. An important part of this within-subject variance can be explained further by the different effects of "antral" or duodenal origin of the preceding phase III. Although Gregersen et al. (6) described a positive correlation between the duration of phase III in the duodenum and the duration of the next MMC cycle, they could not attribute this to a difference in origin of phase III, most likely due to the limited number of observations within each subject. The percentages of "antral" and duodenal originating phases III observed within a subject will strongly affect the mean MMC cycle duration of this subject as well as the overall mean of a group of subjects. An explanation for the differences in MMC cycle duration and duration of phases I and II depending on the origin of the preceding phase III may imply differences in the mechanism controlling interdigestive motility in antrum and small intestine. This may also reflect functional differences.

Differences exist in the hormonal mechanisms involved in the regulation of antral and duodenal phase III. Motilin is a peptide that selectively induces antral phase III activity (1, 3, 25, 30), whereas the peptide somatostatin selectively induces intestinal phase III and even suppresses plasma motilin increase and the occurrence of antral phase III (14, 17). Besides this specific importance of motilin for antral component of the MMC, gastric, biliary, and pancreatic secretion are also coupled specifically to the antral component of the MMC (15, 31). Induction of phase III is subject to a refractory period in which no phase III can be induced (13, 24, 27). From our study we suggest that a difference may exist in the refractory period between the gastric antrum and small intestine, with a shorter duration in the duodenum compared with the antrum. This hypothesis is supported by observations in our laboratory with repeated bolus infusions of motilin (12). We observed that a motilin-induced premature antral phase III only occurred when motilin was infused after a preceding duodenal phase III. When the preceding phase III was of "antral" origin, we could not initiate an antral phase III with motilin. This observation points toward motilin receptor tachyphylaxis with a refractory period of longer duration following a phase III of "antral" origin.

When antral and duodenal motility are regulated by different mechanisms, as we suggested, we would expect a phase III of duodenal origin to occur independently of a previous "antral" starting phase III. However, in our study, the occurrence of a duodenal starting phase III was also delayed after a previous phase III of "antral" origin. It thus seems that after a phase III of "antral" origin a mechanism is present that temporarily inhibits both antral and duodenal phase III activity. Whether this inhibition is of neural origin involving nitricergic neurons with nitric oxide as neurotransmitter is not known. It is also unclear whether inhibition of phase III activity by suppression of both motilin and somatostatin release or receptor tachyphylaxis plays a role.

Besides the described dependency of MMC characteristics on the origin of the preceding phase III, we also observed that the duration of phase III in the duodenum is dependent on the origin of this phase III, with a longer duration when phase III originates in the "antrum" compared with a duodenal origin. This finding confirms previous observations by Gregersen et al. (6). They describe a duration of the duodenal phase III proportional to the preceding antral activity, with the longest duration of the duodenal phase III when preceded by an antral phase III and the shortest duration of the duodenal phase III when preceded by an antral phase I. This difference in phase III duration depending on the start of phase III is an additional argument for a difference in mechanism regulating "antral" or duodenal origin of phase III. A large variation in phase III duration was also described by Husebye et al. (8). We could, however, not confirm the negative correlation between phase III duration and propagation velocity of phase III as they described, possibly due to the great differences between individuals that we accounted for in our model. In our study we also observed greater antral pressure wave amplitudes during phase II when this phase II was followed by a phase III of "antral" origin. This observation can be explained by the high amplitude pressure waves in the antrum during late phase II.

Based on our observations, we hypothesize that the large variation in MMC cycle duration within a subject is based on averaging those MMCs following a phase III of "antral" origin and those following a phase III of duodenal origin. One of the limitations of this study is that we measured for a relatively short period of time in
the lower part of the stomach and the duodenum. It would be very interesting to study the lower esophageal sphincter, proximal stomach, jejunum, and ileum as well to find out whether an “antral” phase III 1) actually starts more proximal and 2) is more frequently and more quickly followed by a phase III originating in the jejunum or in the ileum than observed for the duodenum in the present study.

In conclusion, individual MMC cycle duration and duration of phases I, II, and III are dependent on the place of origin of the preceding phase III, which explains an important part of the within-subject variance. Furthermore, the origin of phase III determines the duration of this phase III. Therefore, knowledge of the origin of phase III is important when MMC characteristics are compared between studies or between healthy subjects and patients. Phase III origin may be an additional factor to consider in clinical research, although consensus on the clinical importance of MMC duration has still not been reached (19).

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