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Editorials

ELECTROGASTROGRAPHY: A SEDUCTIVE PROMISE, ONLY PARTIALLY KEPT

In this issue of the Journal, the paper by Brzana *et al*. (1) shows that electrogastrography (EGG), a technique of recording gastric myoelectric activity (GMA) from the skin surface, is able to differentiate gastroparesis secondary to gastric outlet obstruction from idiopathic gastroparesis. This EGG finding is comparable to the proposed ability of manometry to distinguish partial intestinal obstruction from pseudo-obstruction (2) and represents one of the milestones on the long march of EGG which started in 1922 when Alvarez, inspired by electrocardiography, recorded the GMA for the first time, with cutaneous electrodes. Despite the subsequent demonstration by electromyography (EMG), performed "in vitro" and "in vivo," that the GMA is the "conditio sine qua non" of coordinated motor activity of the stomach, EGG never gained the same widespread acceptance in research and clinical settings, as electrocardiography. The reasons for this ostracism may be traced to the inability of EGG to satisfactorily respond to two fundamental questions repeatedly asked of EGG over the past 30 years, namely, "is EGG really able to record the GMA and what is the diagnostic and therapeutic impact of EGG recordings?"

Does EGG satisfactorily reflect the GMA?

EMG studies have shown that the GMA consists of two components: a slow wave (named also control potential or electrical control activity), which is caused by a rhythmic depolarization of smooth muscle cells, always present even when the contractions are absent, and action potentials (named also spikes or response potential), which appear on the second portion of the slow wave and are an expression of the contraction of the muscular fibres. In the stomach, the slow wave is generated by a pacemaker located near the gastric fundus, at a frequency of approximately 3 cycles per min in humans, and sweeps in the shape of an annular band and with increasing velocity, through the stomach toward the pylorus. The apparent propagation of the slow wave is caused by a "coupling" between slow waves autonomously generated by contiguous groups of smooth muscle cells, whose intrinsic frequency decreases as one moves in an aboral direction and which behave as a chain of relaxation oscillators (3). The slow wave of the more proximal cells that possess a higher frequency "entrains" the more distal ones, thereby establishing a frequency "plateau" of approximately 3 cycles/min in the entire stomach. "Uncoupling" prevents the propagation of slow waves, whereas "retrograde coupling" gives rise to a retrograde propagation of slow waves.

Together with skin-electrode impedance, the distance of the stomach from the skin is the principal cause of the absence of spikes and of the feebleness of the gastric electrical signal, recorded by EGG at the cutaneous level, where the signal also becomes admixed with artefacts generated by electrical activity of cardiac, respiratory, duodenal, and colonic origin as well as by body movement, making some portions of the recording undecipherable. Consequently, the raw tracing must be passed through electronic filters and subjected to automated analysis with the aid of specific programs (fast Fourier transform, running spectral analysis, adaptive spectral analysis, etc). These filters and methods of analysis, however, may remove potentially useful information from the electrical signal (4). Because the EGG is not able to record the spikes, the major indicator of contractile activity is absent. However, many investigators assert that the presence of spikes and related pressure waves is signalled, in the EGG signal, by an increase in amplitude of the slow wave referred to as the EGG power (5). As evidence, they refer to the observation that the EGG power increases after drugs or meals that stimulate motility and decreases after drugs or meals that inhibit motility (6, 7). However, experiments that included simultaneous manometric recordings demonstrated that the EGG is unable to recognize the intense motor activity of phase III of the migrating motor complex, whether spontaneous (8) or induced by cisapride (9). Furthermore, others failed to observe a significant correlation between slow wave amplitude and antral contractions, measured ultrasonographically (10). In addition, the postprandial increase in EGG power, relative to the fasting period, has been explained by the approximation of the antral wall, distended by the meal, to the skin electrodes. Thus, the EGG power also increases when the antrum is distended by a balloon, even as antral contractions are blocked by drugs (11). Finally, it has been established recently that the EGG power is increased by an increase in slow wave propagation velocity and is reduced by slow wave uncoupling (12). In conclusion, EGG is not able to indicate the occurrence of phase III of MMC, whereas the postprandial EGG power increase is only partially caused by an increase in motor activity.

The distance between the skin electrodes and the stomach

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wall is also responsible for the inability of the EGG to record the alterations in both slow wave propagation and "coupling," which may disrupt peristalsis. With the possible exception of individuals with a very thin abdominal wall (13), neither the time-shift between slow waves recorded with a cutaneous electrode over the antrum and another on the corpus, nor the analysis of the dynamics of the EGG wave form permit a determination of slow wave direction (11). Similarly, "uncoupling" between slow waves originating from the proximal and distal antrum is recorded as a slow wave of normal frequency (11, 14). However, an EGG method of analysis capable of recognizing severe electrical "uncoupling" in dogs has been developed recently (15), but needs to be validated in man.

Although the current systems for filtering and analyzing EGG signals are remarkably improved, the ability of the EGG to recognize alterations in slow wave frequency, as tachygastria (>4 cycles/min), bradygastria (>2 cycles/min), tachy- and brady-arrhythmia, complete arrhythmia and electrical silence, is not above questioning. Firstly, EGG running spectrum analysis is unable, for technical reasons, to detect tachygastrias shorter than 64 s in duration (16). Secondly, a comparison of simultaneous recordings from internal and cutaneous electrodes showed that although the EGG is 90% accurate during periods of normal frequency and tachygastria, only 50–70% of "arrhythmias" recorded by EGG corresponds to a true alteration in GMA frequency (14). Other investigators (17), who also found the EGG records more episodes of tachygastria and tachyrhythmia than a concomitant EMG, found that this was most likely to happen when many artefacts are operative. However, an automated method for artefact detection and deletion has been devised recently (18). If these latter technical refinements are truly effective, they may guarantee the detection, by EGG, of clinically relevant alterations in the GMA.

What is the clinical usefulness of EGG findings?

EGG examinations have been performed in various clinical conditions, both organic and functional, characterized by dyspeptic symptoms and, especially, nausea and vomiting, and in the presence and absence of demonstrated alterations in gastric motility. In some cases, EGG was carried out at the same time as the gastric emptying studies or manometric recordings to establish whether the information provided by EGG parallels that provided by these more invasive studies and whether, therefore, EGG might replace them in clinical practice. EGG recordings performed during acute episodes of nausea and vomiting, whether spontaneous as in nausea of pregnancy, or artificially induced by labyrinthine stimulation (6, 7), or by stimulation of duodenal chemoreceptors (19) or rectal distension (20), showed that the appearance of nausea is associated with the onset of gastric dysrhythmias and, especially tachygastria, and that these disappear with the disappearance of nausea. The finding of tachygastria on EGG is of clinical value, given the deleterious effect of this rhythm disturbance on motility: it is frequently propagated orally and is associated with an absence of contractions (21). A lack of motor activity is also observed during other kinds of gastric dysrhythmias, such as tachyrhythmia, bradygastria, bradyarrhythmia, gastric "fibrillation," and electrical silence (22, 23). All these dysrhythmias are frequently found, especially after meals, in patients with gastroparesis, chronic dyspepsia, anorexia nervosa and bulimia, cyclic vomiting syndrome, and other conditions characterized by a delayed gastric emptying (6, 7, 24, 25). In these same instances, an absent or reduced postprandial EGG power increase, attributed to an impaired postprandial gastric motor response, has been frequently documented. Postprandial alterations in EGG rhythm, frequency, and power are considered by many investigators as, more or less, reliable indicators of antral motor dysfunction and delayed gastric emptying (7, 26, 27). Some investigators have, indeed, gone on to propose an automated diagnosis of delayed gastric emptying based on EGG findings using the neural network approach (28). However, this approach could be valid only for gastric emptying delay of idiopathic origin, because in patients with delayed emptying secondary to diabetes, scleroderma or hyperthyroidism, no significant relationship was observed between EGG and gastric emptying (29–32), probably because of different pathophysiological mechanisms. In fact, for example, EGG findings may be significantly influenced in diabetes by the level of glycemia levels (33). However, even in idiopathic gastroparesis, EGG and gastric emptying are not strictly correlated; approximately 25–30% of patients with idiopathic gastroparesis have a normal EGG (27, 34), which might be explained by the presence of, as yet unidentified, extragastric causes (1, 35).

EGG alterations are considered a marker of gastric neuromuscular dysfunction (7) and even have been proposed as able to distinguish visceral myopathy from visceral neuropathy (36). However, it is interesting to note that EGG abnormalities have been documented in patients with idiopathic dyspepsia and with normal gastric emptying (24, 26, 34). On follow-up 1 yr later, dysrhythmias are more likely to persist in those who remain symptomatic, regardless of any changes in gastric emptying (24). In addition, if one considers that the prokinetic drug domperidone improves nausea and tachygastria, but not gastric emptying (30), whereas cisapride may improve gastric emptying, but not influence dysrhythmia and may scarcely affect nausea (37), one may be led to conclude that EGG alterations correlate more with the presence of dyspeptic symptoms than with a delay in gastric emptying.

Conclusion

For the time being, the response to the two questions posed at the onset may remain unsatisfactory for many "motilists," but there is a widespread effort to address the shortcomings of EGG, as can be judged by the increase in the number of abstracts presented at major international congresses and in papers published on EGG. However, the future of EGG rests in

the hands of the electronic engineers, who are alone capable of resolving such fundamental technical problems as the detection of contractions, slow wave propagation and "uncoupling." The potential of this technique is great, because it gives information on the GMA that is directly relevant to gastric motility in both fasting and postprandial periods; it is not invasive, is relatively inexpensive, and easy to perform. It would be a pity, therefore, if EGG cannot emerge beyond the "verge of acceptance as a research and diagnostic tool."

At present, I believe the EGG does not give clinically useful information in organic diseases of the stomach, unless a functional alteration is also present, as exemplified by those gastric ulcer patients who demonstrate tachygastria only when they have nausea and vomiting (38). It is of limited clinical help in hyperemesis gravidarum, motion sickness, cyclic vomiting syndrome, anorexia nervosa, and bulimia, but may have a not insignificant role in the management of functional dyspepsia and idiopathic gastroparesis. In these cases, EGG should be performed, not before or instead of, but after a gastric emptying study. In fact, it may give information more important than a simple indication of "probably delayed gastric emptying" and may help to understand and manage better the alterations in gastric emptying and the dyspeptic symptoms. In a case of delayed gastric emptying, if the EGG is abnormal, a gastric neuromuscular abnormality is likely, and a gastric prokinetic drug is indicated, whereas if the EGG is normal, an extragastric cause such as intestinal hyperdysmotility (35) or, as suggested by the paper by Brzana *et al*., a previously undetected gastric outlet obstruction (1), should be considered; disorders which, of course, would not benefit from stimulation of gastric motor activity. In the dyspeptic patient with normal gastric emptying, abnormal EGG featuring tachygastria could indicate either a central origin for the dyspeptic symptoms, as happens in motion sickness, which may benefit from an antiarrhythmic drug such as domperidone, or an overstimulation of duodenal chemoreceptors (19), whereas a normal EGG may suggest either altered visceral perception or a psychological problem. Further studies alone will establish if this approach of inserting the EGG into the diagnostic algorythm for dyspepsia is valid or illusory.

M. Bortolotti, M.D.
First Medical Clinic
Department of Internal Medicine and Gastroenterology
University of Bologna
Bologna, Italy

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Reprint requests and correspondence: Prof. M. Bortolotti, Via Massarenti 48, 40138 Bologna, Italy.

ABLATION THERAPY OF BARRETT'S ESOPHAGUS: MEASURES OF SUCCESS AND FAILURE

It is now generally accepted that stratified squamous epithelium can reepithelialize ablated metaplastic glandular esophageal tissue (Barrett's esophagus) in an anacid environment (1). But important questions remain. The most fundamental question is: Is restoration of squamous epithelium a reasonable therapeutic goal? Justification for such treatment is based on the notion that elimination of the metaplastic epithelium would effectively reduce complications of the condition, principally adenocarcinoma. The truth of this intuitively self-evident notion, however, has not been proved. It is probably safe to say that ablation therapy would become a standard of care if such proof was established, particularly if it was shown that restored squamous mucosa persisted normally, and surveillance for malignant transformation was not required.

Theoretically, the outcome of ablation therapy will be related to two factors: (1) efficacy of the method of abnormal tissue ablation, and (2) promotion of normal esophageal mucosal regeneration. An ideal ablative technique will uniformly and completely destroy the abnormal epithelium with a single, easy application that is safe, precisely targeted, and of relatively low cost. Of these features, completeness of destruction is most crucial. None of the reported ablative techniques fulfill these ideals. Foci of metaplastic epithelium have commonly been identified beneath restored squamous tissue. There are two possible reasons these foci are found. First, the foci may have escaped destruction. Neither thermal nor photodynamic therapies predictably control the depth and homogeneity of injury. Second, the foci may have been regenerated because conditions necessary for squamous reepithelialization were not established. Little is known about esophageal mucosal repair: cell replication, differentiation, and restitution of mucosal integrity. Squamous tissue regeneration, at least, seems to require an environment free of refluxed gastroduodenal contents (acid, enzymes, bile) and/or inflammation.

In this issue of the journal, Byrne *et al*. present a pilot study assessing the feasibility of Argon Beam Plasma Coagulation (ABPC) destruction of metaplastic and dysplastic esophageal glandular tissue to restore normal squamous lining (2). Thirty patients underwent treatment. Twenty-seven had restoration of squamous tissue. However, patients with long segments were considered to be restored if they had <2 cm metaplastic epithelium remaining in the distal esophagus. Histopathological analysis of four quadrant biopsies taken every 3 cm revealed that 70% of patients had no metaplastic or dysplastic epithelium underlying squamous lining during follow-up periods of 6–18 months. Multiple treatments were required. Retrosternal discomfort and odynophagia were modest, but two perforations occurred, with one death. The authors conclude the technique of ABPC is capable of restoring squamous tissue in Barrett's esophagus, and the treatment may even be successful "in creating total squamous cover." However, they emphasize that, "It is too soon to recommend ABPC for dysplastic or nondysplastic Barrett's because follow-up is too short to show a decreased incidence of and mortality from adenocarcinoma."

Although daunting, a protocol is conceivable to determine the efficacy and safety of ablation therapy. It would require multiple centers, restrictive entry criteria (*e.g.*, ≤ 5 cm), precise execution, rigorous control of reflux (*e.g.*, 24-h esophageal pH monitoring), at least 5-yr follow-up, and use of surrogate markers of neoplasia (*e.g.*, P53 expression). Most importantly, complete squamous restoration would require the absence of intestinal metaplasia at the squamocolumnar border and in jumbo biopsies from four quadrants at 2 cm intervals for 2 consecutive months. With this definition, $>95\%$ but $<100\%$ of the abnormal tissue would likely be eliminated and success, indicated by statistically significant differences between treated and untreated groups, would be evident.

Is it time for this study? Possibly. I am concerned that the measure of failure, adenocarcinoma, might also be evident. This concern reflects limitations of the ablative techniques, and the ability to modify gastroesophageal reflux, esophageal inflammation and repair. New approaches are needed to assure complete ablation—perhaps multimodal, using adjunctive site-directed agents to knock out or modify differentiation of glandular progenitor cells. New approaches are also needed to modify the soluble and insoluble mediators

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