Transmural potential difference in patients with hiatus hernia and oesophageal ulcer¹

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Recordings of transmural potential difference (PD) in the stomach have well established that the mucosal surface of this organ is negative in relation to the serosal surface (Rehm, 1946; Revelstad, Owen, and Magath, 1952). On the other hand, it had been noted that the oesophagus has a positive transmural potential difference (Helm, Schlegel, Code, and Summerskill, 1965). The potential difference transition zone from negative to positive values was shown to represent the mucosal transition from acid-bearing to columnar and from columnar to oesophageal mucosa (Meckeler and Ingelfinger, 1967). Utilizing an improved method of recording transmural potential difference (Hernandez and Beck, 1968), we reexamined the characteristics of the potential difference transition zone in normal individuals and in patients suffering from hiatus hernia. In addition, we explored the variations in potential difference which occur over lesions where the mucosal integrity of the oesophagus was destroyed by ulcerations.

METHODS

RECORDING OF POTENTIAL DIFFERENCE SIMULTANEOUSLY WITH OESOPHAGEAL PRESSURE MEASUREMENTS ('PULL-THROUGH METHOD') Oesophageal pressure and potential difference were measured by a technique previously described and evaluated (Hernandez and Beck, 1968), and measurements of pressure changes were based on the method of Winans and Harris (1967). The main features of the combined method are depicted in Figure 1.

For both the pressure and the potential difference recording, Ringer's solution ($\text{Na}^+ = 147$ m-equiv/l; $\text{K}^+ = 4$ m-equiv/l; $\text{Ca}^{++} 4.5$ m-equiv/l and $\text{Cl}^- = 156$ m-equiv/l) was infused at a rate of 0.382 ml/min. The 50 ml plastic syringes were filled through a three-way plastic stopcock (SC) and placed into a Harvard pump² (HP) which slowly advanced the plungers. Three of the

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FIG. 1. Schematic representation of the method for combined potential difference and pressure measurement in the 'pull-through' experiments.

- A = Orifice for proximal motility catheter
- B = Orifice for middle motility catheter
- C = Orifice for distal motility catheter
- E = Ag/AgCl electrode
- HP = Harvard pump
- Pc = Plastic container for electrode filled with Ringer's solution
- PD = Orifice for potential difference measurement
- Pn = Pneumograph
- R = Recorder
- Ref = Plastic container for electrode and finger
- SC = Three-way stopcock
- Scar = Scarification on finger
- T = Transducer
- VM = Voltmeter

syringes were connected by means of polyvinyl tubings to Statham transducers¹ (T), and the fourth syringe to a plastic container (Pc) which held an Ag/AgCl electrode² (E). Attached to the transducers and the plastic container was a 90 cm-long, four-channel catheter bundle made of polyvinyl tubing (OD = 0.065; ID = 0.044³) glued together with tetrahydrofurane. Three of the tubes served to transmit pressure changes and the fourth to contain the electrolyte bridge for recording the potential difference. One side opening 3 mm long was made in each tube (A, B, C, and PD) and the portion of the catheter below the orifice was plugged. The most distal orifice (C) was 1 cm proximal to the end of the catheter bundle. The middle pressure recording orifice (B) was 4 cm and the most proximal recording site was 8 cm above C. Potential difference was measured between the scarified skin and the intraluminal mucosa. Contact with the mucosa was made through the side opening (PD) placed at the same level as B. The measuring half circuit consisted of Ag/AgCl electrode (E) dipped into the plastic container (Pc) filled with Ringer's solution. By means of the continuous infusion technique, this solution provided an electrolyte bridge to the luminal mucosa. In the reference half circuit (Ref), a similar electrode (E) dipped into Ringer's solution was used. This electrode was in electrolytic contact with the subcutaneous tissue through the scarified skin of the subject's left index finger. The two half circuits were connected to a voltmeter (VM).⁴ The output of the voltmeter and the transducers was constantly monitored on a multichannel recorder (R).⁵ After expulsion of air from the system, before each study, the transducers and voltmeter were calibrated and the two half circuits balanced. To avoid external grounding of the circuit, only plastic syringes, stopcocks, and connexions were used. Care was taken that short circuiting should not occur through the electrolyte solution leaking. Respiration was recorded by means of a pneumograph attached to the chest of the subject (Pn). During the study, the catheter bundle was gradually withdrawn at stages of 1 cm from the stomach into the oesophagus.

MEASUREMENT OF THE POTENTIAL DIFFERENCE DURING OESOPHAGOSCOPY ('DIRECT TRANSOESOPHAGOSCOPIC METHOD') The Eder-Hufford oesophagoscope (Hufford, 1949) was insulated with a plastic coating. The oesophagoscopic insert recently described by Beck (1968) was passed through the oesophagoscope. This permitted good visualization as well as the taking of biopsies at the same site where the potential difference was measured. To measure the potential difference, an exploring electrode was made of 0.065 ID, 0.044 OD, polyvinyl tubing⁶ filled with 1% agar dissolved in Ringer's solution. The distal end of the 'potential difference probe' was then passed through the oesophagoscopic insert by means of a special channel constructed for this purpose. Thus, any

FIG. 2. Diagram of circuit for 'direct transoesophagoscopic measurement of oesophageal transmural potential difference.'

Oesophagoscope Eder-Hufford oesophagoscope covered with plastic sheet.

Insert Described in detail by Beck (1968)

A = Reference Scarified finger dipped into Ringer's electrode solution

B = Exploring Polyvinyl tube filled with 1% agar in Ringer's solution passed through oesophagoscopic insert.

Voltmeter Beckman expandomatic pH meter.

Recorder Beckman Offner recorder.

lesion to be explored in the oesophagus could be touched with the probe under direct vision. The proximal end of the probe protruded from the oesophagoscope and was dipped into a container filled with Ringer's solution. From here on, both half circuits were used for recording potential difference were similar to that described above for recording non-endoscopic potential difference. The scarified skin served as the reference point. Figure 2 demonstrates the circuit used in recording the potential difference under direct vision.

As long as the physical contact of the exploring electrode and the mucosa of the oesophagus was maintained, this method provided steady and reproducible recordings of potential difference. If the contact was accidentally interrupted while moving the oesophagoscope, a waiting period of about one minute was required after re-establishing contact before a steady reading could be again obtained. When an oesophageal ulcer was endoscopically discovered, the potential difference of the mucosa below the lesion was measured. Then the endoscope was slowly withdrawn, so that the exploring electrode lay over the ulcerated area. After this, the potential difference above the ulcer was measured. This was always repeated to confirm the original findings. A biopsy was then taken to assess the nature of the lesion.

HIATUS HERNIA STUDY

CLINICAL SUBJECTS Thirteen normal subjects of

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³Beckton, Dickinson & Rutherford, New Jersey.

⁴Beckman Expandomatic pH meter (model 76-A).

⁵Beckman Offner type R dynograph.

⁶Beckton, Dickinson & Rutherford, New Jersey.

21 to 51 years of age served as controls. These subjects had no gastrointestinal symptoms and were radiographed to exclude asymptomatic hiatus hernia. Fourteen patients between the ages of 17 and 61 who had symptoms and radiological evidence of hiatus hernia served as the experimental group.

PLOTTING OF DATA AT THE OESOPHAGOGASTRIC JUNCTIONAL AREA To correlate pressure changes and the potential difference at the oesophagogastric junctional area, data were plotted in two different ways. First the potential difference was correlated against the respiratory pressure reversal point ($= 0$ cm) on the corresponding motility tracing. This method is similar to that previously used by others (Helm *et al*, 1965; Scobie, Schlegel, Code, and Summerskill, 1965). Since Harris and Pope (1966) demonstrated that the respiratory pressure reversal is not a constant reference point inasmuch as its level may vary from experiment to experiment, a more stable point of reference was looked for. In an alternate method of plotting, the beginning of the high pressure zone (0 cm) observed on the corresponding pressure tracing was taken as the point of reference. This is similar to that we have already used (Hernandez and Beck, 1968).

STUDY OF PATIENTS WITH OESOPHAGEAL ULCERS

CLINICAL SUBJECTS The tracings of the potential difference obtained in the body of the oesophagus of 10 healthy subjects served as controls for the 'pull-through' experiments. The oesophageal potential difference of these subjects was analysed from 2 cm proximal to the end of the potential difference transition zone up to 2 cm below the high pressure

zone of the upper oesophageal sphincter. Ten cases of ulceration of the body of the oesophagus were studied. They were diagnosed radiologically and by oesophagoscopy or by oesophagoscopy alone. The size and location of these lesions varied from patient to patient. In all cases, change in potential difference over the ulcer was studied by both the 'pull-through' and the 'direct transoesophagoscopy' method. This study deals only with ulcers in the body of the oesophagus. Oesophagogastric junctional ulcers were not studied for technical reasons.

RESULTS

HIATUS HERNIA STUDY A typical potential difference transition zone from negative gastric to a positive oesophageal potential difference is shown in Figure 3. In B, the beginning of the high pressure zone is at 38 cm and the respiratory pressure reversal point at 36 cm. The potential difference transition zone starts at 37 cm and ends at 35 cm. It is 2 cm long. It begins at $+1$ cm if 0 cm is equal to the high pressure zone, and at -1 if 0 cm equals the respiratory reversal point. The mean potential difference transition zones of 13 normal subjects and 14 patients with hiatus hernia are plotted against the respiratory reversal point in Figure 4. This figure demonstrates that the potential difference transition zone of patients and normals starts at the same level distally, *ie*, at -3 cm. Proximally, the mean transition zone of normals is completed at 2 cm above the respiratory pressure reversal point. In the group of patients, the mean potential difference reaches its maximal level at 4 cm above the respiratory pressure reversal point. This indicates that the mean potential difference transition zone is longer in

FIG. 3. Combined motility and potential difference record at the potential difference transition zone area ('pull-through' technique).

FIG. 4. Mean potential difference transition zone of 13 normal subjects and 14 patients with hiatus hernia plotted against the point of respiratory pressure reversal.

FIG. 5. Mean potential difference transition zone of 13 normal subjects and 14 patients with hiatus hernia plotted against the beginning of the high pressure zone.

FIG. 6. Length of potential difference transition zone in centimetres.

FIG. 7. Midpoints of potential difference transition zone plotted against the beginning of high pressure zone.

the patient group than in the normal controls ($P < 0.01$). The same data plotted against the beginning of the high pressure zone are shown in Figure 5. This figure demonstrates that similar lengthening and upward shift of the potential difference transition zone in the patients' group was also demonstrated when data were plotted against the beginning of the high pressure zone ($P < 0.01$). Although the mean difference in length of the transition zone and its shift in the oral direction in patients with hiatus hernia is statistically significant, the data obtained in individual patients and normals overlap. Figure 6 demonstrates the individual data of the length of the transition zone. The mean for normals is 3.2 cm and for patients with hiatus hernia 5.8 cm. The difference is significant ($P < 0.001$). Figure 7 shows the level where the individual potential difference transition zones reach their 50% rise when plotted against the beginning of the high pressure zone. This difference is significant ($P < 0.01$), but again there is considerable overlap of the data for individuals.

STUDY OF PATIENTS WITH OESOPHAGEAL ULCERS
'Pull-through' potential difference studies in 10 normal subjects demonstrated that all such readings along the body of the oesophagus were positive (mean $\pm$ SE = 8.2 ± 1.3 mV). Although different individuals varied from each other in all of the subjects, the tracings were straight. The maximal change along the body of the oesophagus was less than 5 mV in the same individual. In contrast to the above finding, of the 10 patients with ulcerating

lesions of the body of the oesophagus, seven demonstrated a sharp fall in excess of 5 mV at the level of the ulcer. In two out of seven cases, the oesophageal potential difference became negative over the ulcer. Figure 8 demonstrates a combined potential difference and pressure tracing using the 'pull-through' method in a patient who had an oesophageal ulcer at 22 cm below the alveolar line.

The potential difference was measured during oesophagoscopy in all 10 cases of ulcers of the body of the oesophagus. Although the method was found to lend itself well to correlating transmural potential difference with visual and histological findings in the body of the oesophagus, this was not the case in the area of the oesophagogastric mucosal junction. Using this method, the readings for potential difference in this area were erratic, and therefore ulcers of the oesophagogastric junctional area were not studied. In the body of the oesophagus a negative deflection over the ulcerated area was noted in all 10 cases. Figure 9 demonstrates such a fall in a patient with a benign ulcer ($1\frac{1}{2}$ cm diameter) in the midoesophagus.

Table I summarizes the results obtained by 'pull-through' and 'transoesophagoscopic' recordings of the potential difference.

TABLE I

No.	Negative Deflection in Excess of 5 mV		
	'Pull-through'	Direct	Method
Controls	10	0	—
Oesophageal ulcer	10	7	10

FIG. 8. Motility and potential difference recording in a patient with ulcer of the upper oesophagus using the gradual 'pull-through' method. The arrangement in this figure is similar to that of Figure 3. Note the fall of potential difference at 22 centimetres.

FIG. 9. Transoesophagoscopy recording of potential difference over a benign ulcer.
Horizontal line = 0 level.
Baseline reading above and below lesion = +8 mV.
Maximal drop = 12 mV over ulcer.

DISCUSSION

Our experiments using the potential difference 'pull-through' method demonstrated that the transition zone from negative gastric to positive oesophageal potential difference was increased in length and was proximally dislocated in patients with hiatus hernia. In addition, utilizing both the 'pull-through' and the direct 'transoesophagoscopy' potential difference method, we have shown that the potential difference in the body of the oesophagus of normal subjects is stable. A negative deflection was demonstrated over ulcers in the body of the oesophagus. Direct transoesophagoscopy measurements of potential difference had to be restricted to the body of the oesophagus since these could not be carried out accurately in the area of the potential difference transition zone of the oesophagogastric junction. Using this method, results in this region were erratic, presumably due to abrasion of the mucosal surface when the oesophagoscope was manipulated through the hiatus.

Our findings of an increase in length and proximal dislocation of the potential difference transition zone in patients with hiatus hernia obtained with an improved method (Hernandez and Beck, 1968) confirmed and further elucidated the results of Helm and his associates (1965). Meckeler and Ingelfinger (1967) demonstrated that the potential difference transition zone from negative to positive denotes mucosal transition from acid-bearing to columnar cardiac or from cardiac to oesophageal mucosa. Accordingly, the upward shift of the transition zone could be explained by a dislocation of the mucosal oesophagogastric junction in relation to the diaphragmatic hiatus, *ie*, the point of respiratory reversal recorded on the motility record. Lengthening of the mean potential difference transition zone could be the result of variation in the size of the hernias of different patients. In some

subjects, where the hernia is small or fully reduced, the potential difference transition zones could start and end at the same level as in normal individuals while in patients who had large hernias the transition zone could start and end more proximally to the mouth. Such a variation would no doubt result in an upward shift and prolongation of the mean transition zone. This explanation, however, is valid only if the data are plotted against the hiatus. But considerable doubt exists as to the validity of equating the respiratory reversal with the anatomical hiatus (Harris and Pope, 1966). The explanation of the upward shift offered above becomes untenable if the data plotted against the beginning of the high pressure zone are taken into consideration. The high pressure zone is thought to denote the lower oesophageal sphincter (Atkinson, 1962; Code, Creamer, Schlegel, Olsen, Donoghue, and Andersen, 1958) and the transition zone, the mucosal oesophagogastric junction (Meckeler and Ingelfinger, 1967). When a hiatus hernia moves up into the chest, theoretically the mucosal oesophagogastric junction and the lower oesophageal sphincter should move in parallel. Dissociation of the levels of the high pressure and the potential difference transition zones in patients with hiatus hernia can only be explained if (a) the potential difference transition zone does not represent the mucosal oesophagogastric junction; (b) if the high pressure zone does not represent the lower oesophageal sphincter; (c) if in some patients with hiatus hernia the gastric mucosa invades the lower oesophagus (Allison and Johnstone, 1953); or (d) if the potential difference is prevented from reaching its normal positive level in the lower oesophagus due to inflammation or ulceration of this area. In this case, the potential difference reaches normal levels, only higher up in the oesophagus where the mucosa is normal. Our experiments do not provide proof for either of the above-mentioned possibilities but there is reasonable basis for speculation. On the basis of the biopsy data of Meckeler and Ingelfinger (1967), it is unlikely that the potential difference transition zone should not represent the mucosal oesophagogastric junction. Code and his associates (1962) have postulated that in some patients with small hiatus hernias, the lower part of the high pressure zone does not represent the lower oesophageal sphincter. They suggest that this part of the high pressure zone may result from gastric mucosal folds being 'stuffed' into the hiatus. This theory may explain the upward shift of the potential difference transition zone when plotted against the beginning of the high pressure zone and our experiments may be considered as lending support to Code's concept (Code, Kelly, Schlegel, and Olsen, 1962). Although this may explain the

upward shift of the potential difference transition zone, it does not provide an explanation as to why the individual potential difference transition zones are prolonged in about half of our patients with hiatus hernia. It is possible, however, to speculate that in these cases the prolongation of the potential difference transition zone is the result of inflammation or ulceration in the lower oesophagus or invasion of the oesophagus by gastric mucosa. Any of these reasons would lower the oesophageal potential difference and if this lowering occurs at the upper end of the potential difference transition zone, the transition zone will appear increased in length. Indeed, in three out of six patients with long potential difference transition zones there was oesophagogastric ulceration and in two there was severe oesophagitis.

In none of our 13 normal subjects did the potential difference transition zone exceed 5 cm in length and therefore one of more than 6 cm appears to be diagnostic for hiatus hernia. The overlap of length of the normal and abnormal potential difference transition zones in the lower ranges, however, diminishes the value of this finding as a diagnostic tool. A normal potential difference transition zone does not exclude hiatus hernia.

Measurement of transmural potential difference in the body of the oesophagus has not been systematically studied previously. Helm *et al* (1965) and Scobie *et al* (1965) failed to obtain reproducible oesophageal potential differences in patients with various diseases. They ascribed their failure to the inherent difficulties in the method which often led to disruption of the contact and short circuit. Only after a simpler and more reproducible method was devised (Hernandez and Beck, 1968) could the present study be performed. Our data indicate that the transmural potential difference falls over ulcerating lesions of the oesophagus. The findings obtained using the 'pull-through' method done in conjunction with oesophageal motility tracings gained in their significance by confirmation of this fall under direct vision during oesophagoscopy.

In the stomach the potential difference is related to Cl^- , H^+ , and Na^+ exchange (Hogben, 1955; Kitahara, 1967). The mechanism whereby the potential difference is produced in the oesophagus was never studied but is presumably also generated by electrolyte secretion. The absence of mucosa in an ulcer probably acts as an 'electrical hole' resulting in the absence of mucosal potential difference. Since in three out of 10 cases of benign ulcerations, the 'pull-through' method did not demonstrate an appreciable fall, we believe that whether a change in potential difference can be detected over a mucosal

'hole' using the 'pull-through' method must depend on the size of the lesion. It is possible that if a lesion is small, as was the case in the three cases referred to, the potential difference of the surrounding normal mucosa obliterates the negative deflection. This concept is confirmed by the finding that, using direct transoesophagoscopy potential difference recording where the ulcer itself was touched with the exploring electrode, the fall in potential difference was demonstrated in all cases, including the three where the 'pull-through' method failed.

SUMMARY

Using a constant infusion method, transmural potential difference was investigated in patients with hiatus hernia and ulcers of the oesophagus. The potential difference transition zone from negative to positive at the oesophagogastric junction in patients with hiatus hernia was compared to that found in normals. The transition zone is increased in length and is proximally dislocated in patients with hiatus hernia. A fall in potential difference was observed over mucosal ulcerations of the body of the oesophagus using the constant infusion technique. This latter finding was confirmed by measuring the potential difference during oesophagoscopy. In the discussion, it is postulated that the lengthening and upward dislocation of the potential difference transition zone is the result of inflammation and ulceration or possibly invasion by gastric mucosa of the lower oesophagus. It is suggested that the negative deflection over an ulcer in the body of the oesophagus is the result of the absence of mucosa creating an 'electrical hole'.

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