Impairment of epithelial transport but not of barrier function in idiopathic pouchitis after ulcerative colitis

A J Kroesen, M Stockmann, C Ransco, J D Schulzke, M Fromm, H J Buhr

Gut 2002;50:821–826

Background and aims: Little is known of the permeability of ileoanal pouches. Hence the aim of the present study was to determine changes in permeability and mucosal function after ileo-pouchanal anastomosis (IPAA) in patients with ulcerative colitis.

Materials and methods: Biopsies were taken from 43 patients [male:female ratio 28:15; mean age 35.2 (12.5) years] prior to colectomy (ileum prior to pouch), prior to closure of ileostomy (deviation), and after closure of ileostomy (intact pouch) in the case of pouchitis, and from 14 healthy controls. Tissues were mounted in a miniaturised Ussing chamber. Epithelial and subepithelial resistance was determined by transmural impedance analysis. Active Na⁺-glucose cotransport was measured as change in short circuit current after stepwise addition of glucose, and active Cl⁻ secretion was measured after stimulation with theophylline and prostaglandin E₂.

Results: Neither epithelial resistance nor mannitol fluxes were significantly altered compared with intact controls, indicating no barrier defect in pouchitis. Subepithelial resistances of intact pouches and pouchitis were increased compared with deviation (18.2 (1.6) and 24.3 (1.5) v 13.6 (1.0) Ω•cm²) consistent with an adaptive thickening of the subepithelial layer. In contrast, active Cl⁻ secretion of pouchitis tissues was reduced versus intact pouch and controls (1.6 (0.3) v 4.3 (0.7) and 4.6 (0.7) µmol/h/cm²), and Na⁺-glucose cotransport of pouchitis was reduced compared with intact pouch and controls (1.8 (0.5) v 4.2 (0.8) and 8.8 (1.3) µmol/h/cm²).

Conclusions: Ileal mucosa in pouchitis and terminal ileum prior to IPAA exhibit impaired secretory and absorptive transport functions whereas the epithelial barrier function remains unchanged. This differs from findings in ulcerative colitis. Thus the hypothesis that pouchitis represents a remanifestation of ulcerative colitis has to be questioned.

Protocolectomy with an ileoanal pouch anastomosis (IPAA) has become the method of choice for the surgical treatment of ulcerative colitis (UC). Patients are cured of UC after this procedure. Unfortunately, this surgery has a high morbidity both in the early postoperative period as well as in the longer term.¹² The most serious long term complication is an inflammation of the ileoanal pouch (pouchitis). The incidence is high: at the Mayo Clinic³ the cumulative percentage of colitis patients who had developed at least one episode of pouchitis over a mean period of eight years after IPAA was 32%; 39% had a single acute episode that responded to treatment with antibiotics and the remaining 61% had at least one recurrent episode and 7% of these patients had chronic pouchitis.⁴ Sandborn et al introduced in 1994⁴ a pouchitis disease activity index which consists of the parameters clinical symptoms, endoscopic findings, and histology. This scoring system provides simple, objective, sensitive, and quantitative criteria for pouchitis classification.

The aetiology of pouchitis is still unknown. Pouchitis may result from several causes: outflow obstruction of the pouch; persistence of diseased ileal or rectal mucosa; stasis in the pouch with bacterial overgrowth⁵; insufficient short chain fatty acids in the pouch lumen; excessive release of inflammatory mediators; pouch ischaemia; and surgical factors. Although pouchitis has to be considered as a single clinical entity, there are many indicators that indicate that pouchitis is a remanifestation of UC in the ileum.

Alterations in mucosal permeability of the different stages of ileoanal pouches have not characterised to date. There is one publication by Merret and colleagues¹¹ describing this problem.¹² Cr-EDTA was administered into the pouch, and urinary recovery over 24 hours was taken as an indicator of permeability (barrier function). Histological analysis of pouch biopsy specimens was undertaken. Pouchitis was associated with increased permeability (5.9% of administered dose absorbed) compared with that of a healthy pouch. They also found that despite the presence of chronic inflammation in the mature pouch, functional adaptation with reduced permeability occurred in association with colonic metaplasia. An experimental study from our own group characterised the changes in mucosal barrier and transport function after ileal J pouch formation in the rat.¹³ In the Ussing chamber reduced Na⁺-glucose cotransport and impaired electrogenic Cl⁻ secretion were found whereas the epithelial barrier remained unchanged. The status of pouchitis and the pouch with protective ileostomy could not be examined in that study.

In the present study, we characterised epithelial barrier function of the ileal pouch mucosa intraoperatively, prior to pouch formation, and under conditions of diversion by an ileostomy, in the intact pouch, and in pouchitis. The specimens were obtained endoscopically by macro biopsy forceps. Barrier function was examined by transmural impedance analysis and mannitol flux measurements. Transport function was assessed by Na⁺-glucose cotransport and electrogenic Cl⁻ secretion. We found that epithelial transport function, but not barrier function, was impaired in idiopathic pouchitis after UC.

Abbreviations: IPAA, ileoanal pouch anastomosis; UC, ulcerative colitis; PDAI, pouchitis disease activity index; Iₚₒ, short circuit current; R, resistance.
MATERIAL AND METHODS

Patients
The ileums from right sided hemicolectomies for non-stenosing ascending colon cancer (n=14, male:female ratio 6:8) served as healthy controls (group 1). All tissues were obtained from UC patients. Biopsies were taken from 43 patients (male:female ratio 28:15; mean age 35.2 (12.5)). Table 1 summarises the different sites and stages of the specimens. Group 2 tissues were taken during colectomy, just right of the excision well perfused ileum. Seven of these tissues showed histological signs of backwash ileitis. Medical therapy prior to colectomy included: no therapy (colitis carcinomas), four patients; 5-aminosalicylates, 12 patients; prednisolone <20 mg, four patients; prednisolone >20 mg, six patients; and prednisolone and 5-aminosalicylates, 10 patients. The median Truelove score of the simultaneously excised colon was 2.63 (0.15).30 Group 3 specimens were obtained, on average, three months after pouch formation prior to closure of the ileostomy. Intact pouch biopsies (group 4) were taken after a mean of 10 (range 4–24) months after closure of the ileostomy. Three of the pouches were younger than one year. Pouchitis (group 5) was defined by the pouchitis disease activity index (PDAI) from the Mayo Clinic.1 All tissues were obtained prior to medical therapy. For pouchitis and in all patients it was the first manifestation of pouchitis after pouch formation. Pouchitis occurred in this group after a mean of 8 (range 6–26) months. To score ileal tissues, the histological section of the PDAI was selected as this is the only applicable score. Usual UC scores only examine colonic inflammation but in this study the tissue of interest was the terminal ileum. A tissue was defined as affected by pouchitis at a histological PDAI of >6.

Tissue preparation
All specimens obtained were taken endoscopically with a biopsy forceps of 3.4 mm in diameter. The biopsy loci were at the pouch corpus between the two side-to-side anastomoses. In the case of pouchitis, biopsies were taken from the maximal inflamed pouch sites well away from the anastomosis. The specimens were immediately transported to the laboratory in an oxygenated bathing solution at 4°C. Under a dissection microscope, biopsy specimens were spread out and a support disk with a central opening (diameter 1 mm) was glued on the serosal side using Histocryl tissue glue (B Braun, Melsungen, Germany). The disk holding the tissue was then inserted into a special container and mounted between the two halves of an Ussing-type chamber. The exposed tissue area in this chamber was 0.05 cm². All characteristics necessary for alternating current impedance analysis as well as conventional short circuit current and flux measurements were provided in this design. Details of this method have been described previously.13 The time between endoscopic biopsy and mounting of the tissue was less than 30 minutes.

Solutions
The bathing solution for the flux experiments contained (in mmol/l): Na+ 140; Cl− 123.8; K+ 5.4; Ca2+ 1.2; Mg2+ 1.2; HPO42− 2.4; H2PO4− 0.6; HC03− 21; d (+) glucose 10; d (+) mannose 10; glutamine 2.5; and β-OH-butyrate 0.5.26 The solution was gassed with 95% O2 and 5% CO2; temperature was maintained at 37°C using water jacketed reservoirs. The pH of the solution was 7.4 in all experiments. Antibiotics (50 mg/l azlocillin and 4 mg/l tobramycin) served to prevent bacterial overgrowth and had no effect on short circuit current (Isc) in the concentrations used.17 18 Bumetanide, prostaglandin E2, and theophylline were obtained from Sigma Chemical Co. (St Louis, Missouri, USA). If not stated otherwise, drugs were added to the serosal side. 1H mannitol was obtained from Du Pont de Nemours (Wilmington, Delaware, USA).

Alternating current impedance analysis
As previously described, the transmural impedance analysis technique allows differentiation between the epithelial (R′e) and subepithelial (R′sub) portions of total wall resistance (R′t).19 20 The voltage responses after transepithelial application of 35 pA/cm² effective sinewave AC of 48 discrete frequencies ranging from 1 to 65 kHz were detected by phase sensitive amplifiers (model 1250 frequency response analyser and model 1286 electrochemical interface; Solartron Schlumberger, Farnborough, Hampshire, UK). Impedance values were calculated and corrected for the resistance of the bathing solution and the frequency behaviour of the measuring setup for each frequency. For each specimen, the impedance locus was then plotted in a Nyquist diagram and a circle segment was fitted by least squares analysis. From this circle segment, three variables of an electric equivalent circuit were obtained that consisted of a resistor and a capacitor in parallel, representing the epithelium, and a resistor in series with this unit, representing the subepithelium. Because of the frequency dependent electrical characteristics of the capacitor, R′e is obtained at low frequencies whereas R′sub is obtained at high frequencies. R′e was calculated as R′t=R′e−R′sub.

Mannitol fluxes
Mucosal barrier function under the different pouch conditions and UC controls was determined by measurement of unidirectional mucosal to serosal fluxes of 1H mannitol. Also, these experiments were performed under short circuit conditions, as described previously.19

Electrogenic chloride secretion
For measuring electrogenic Cl− secretion, tissues were stimulated by prostaglandin E2 (10−9 mol/l, serosal side) and theophylline (10−5 mol/l, both sides). The increase in Ise (ΔIsc) was measured thereafter. After reaching steady state the effect of theophylline and prostaglandin E2 was antagonised by theophylline (10−4 mol/l) and the decrease in Isc was measured, ΔIscmax (maximum velocity (Vmax)) and Michaelis constant (Km) were determined from Eadie-Hofstee plots for each tissue specimen and ΔIscmax and Km calculated for each experimental group.

Na+–glucose cotransport
For measuring glucose dependent sodium absorption, a glucose free solution was used.25 26 Then, aliquots of standard medium supplemented with 3-O-methyl-glucose were added at 10 minute intervals, resulting in final concentrations of 4, 8, 16, 32, and 48 mmol/l. ΔIscmax and Km were determined from the reciprocal plot (Lineweaver-Burk) for each specimen. For each experimental group, mean (SEM) values for ΔIscmax and Km were calculated. Finally, ΔIs values for each glucose concentration and ΔIscmax values were corrected for the contribution of subepithelial resistance by multiplying by the respective correction factor, which owing to error propagation also accounts for the magnitude of the SEM of these variables.

Histological analysis
Conventional histology was performed on the same tissue specimens as used in the electrophysiological experiments using haematoxylin-eosin stained thin sections. The degree of

Table 1 Site and status of the specimens

<table>
<thead>
<tr>
<th>Group</th>
<th>Biopsy site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Terminal ileum</td>
<td>Healthy control</td>
</tr>
<tr>
<td>2</td>
<td>Terminal ileum</td>
<td>Ileum prior colectomy</td>
</tr>
<tr>
<td>3</td>
<td>Pouch corpus</td>
<td>Deviation</td>
</tr>
<tr>
<td>4</td>
<td>Pouch corpus</td>
<td>Intact pouch</td>
</tr>
<tr>
<td>5</td>
<td>Pouch corpus</td>
<td>Pouchitis</td>
</tr>
</tbody>
</table>
inflammation was scored by the PDAI which allocates 1 score point for mild, 2 for moderate plus crypt abscess, and 3 for severe plus crypt abscess, and 1 score point for <25%, 2 for 25–50%, and 3 for >50% of ulcerations per low power field (mean).

Statistical analysis
Results are given as means (SEM). The Student-Newman-Keul’s test was used for multiple comparisons when the null hypothesis was rejected by Friedman’s test. p<0.05 was considered significant.

RESULTS
Alternating current impedance analysis
Results and statistical evaluation of the impedance analysis are shown in table 2. R’ remained unchanged in the five groups. R’(0) was increased in the ileum of patients with colitis (25.9 (3.4) Ω×cm²), an intact pouch (18.2 (1.6 Ω×cm²)), and pouchitis (24.3 (1.5 Ω×cm²)) compared with deviation (13.6 (1.0) Ω×cm²) and controls (19.3 (3.7) Ω×cm²). Regarding total resistance, a decrease in deviation pouch compared with ileum colitis (28.1 (2.7) Ω×cm²) v 41.0 (3.3) Ω×cm²) was noted.

Mannitol fluxes
Results and statistical evaluations are shown in table 2. No significant differences were found between the five groups, excluding controls. Compared with controls, an increase in porosity was found only in the deviation group (413.7 (38.3) v 207.5 (30.7) nmol/h/cm²).

Electrogenic chloride secretion
Maximum transport capacity of electrogenic chloride secretion was determined from the increase in ISC after administration of theophylline and prostaglandin E₂ (fig 1). Reduction in transport function was found in pouchitis (1.4 (0.3) μmol/h/cm²) and in the ileum colitis group (1.4 (0.2) μmol/h/cm²) compared with the control (4.6 (0.9) μmol/h/cm²), deviation (2.3 (0.5) μmol/h/cm²), and intact pouch (4.3 (0.7) μmol/h/cm²) groups. After application of bumetanide values in all groups were restored to initial values.

Na⁺-glucose cotransport
In the different stages of pouch ileum, the 3-o-methyl-glucose dependent increase in Iᵥ showed saturation. Data and statistical analysis are given in figs 2 and 3. The data in the reciprocal plot fitted a straight line, indicating Michaelis-Menten kinetics. In detail, we observed reduced Na⁺-glucose cotransport in pouchitis compared with the intact pouch (1.8 (0.5) v 4.2 (0.8) μmol/h/cm²) and a reduction in all stages compared with controls. After adding chloridazon, Iᵥ values were restored to values prior to 3-o-methyl-glucose administration (controls 1.8 (0.4) μmol/h/cm²; ileum colitis 2.0 (0.3) μmol/h/cm²; intact pouch 3.0 (0.3) μmol/h/cm²; deviation 1.6 (0.3) μmol/h/cm²; pouchitis 1.8 (0.3) μmol/h/cm²).

Table 2  Transmural electrical resistance and mannitol fluxes

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>R’ (Ω×cm²)</th>
<th>R’(0) (Ω×cm²)</th>
<th>Rₚ (Ω×cm²)</th>
<th>Mannitol flux (nmol/h/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>14</td>
<td>34.6 (4.7)</td>
<td>15.3 (1.0)</td>
<td>19.3 (3.7)</td>
<td>207.5 (30.7)</td>
</tr>
<tr>
<td>Ileum prior colectomy</td>
<td>16</td>
<td>41.0 (3.3)</td>
<td>15.1 (1.4)</td>
<td>25.9 (3.4)</td>
<td>285.0 (47.2)</td>
</tr>
<tr>
<td>Deviation</td>
<td>15</td>
<td>28.1 (2.7)</td>
<td>14.5 (2.3)</td>
<td>13.6 (1.0)</td>
<td>413.7 (38.3)</td>
</tr>
<tr>
<td>Intact pouch</td>
<td>12</td>
<td>33.6 (1.8)</td>
<td>17.4 (1.2)</td>
<td>18.2 (1.6)</td>
<td>280.1 (31.8)</td>
</tr>
<tr>
<td>Pouchitis</td>
<td>14</td>
<td>39.8 (2.0)</td>
<td>15.5 (1.5)</td>
<td>24.3 (1.5)</td>
<td>294.9 (46.8)</td>
</tr>
</tbody>
</table>

*p<0.05 versus deviation and control groups; †p<0.05 versus control group; ‡p<0.05 versus ileum colitis group.

* R’, total resistance; R’(0), epithelial resistance; Rₚ, subepithelial resistance.

Figure 1  Electrogenic Cl⁻ secretion in the five study groups. Maximum short circuit current (Iᵥ) after administration of theophylline and prostaglandin E₂. *p<0.05 versus the control group; †p<0.05 versus the intact pouch group.

Figure 2  Sodium-glucose cotransport in the five study groups. *p<0.05 versus the control group; †p<0.05 versus the intact pouch group. Iᵥ, short circuit current.

Figure 3  Kinetics of sodium-glucose cotransport are dependent on saturation kinetics. *p<0.05 versus the control, ileum colitis, intact pouch, and deviation groups; †p<0.05 versus the control and ileum colitis groups. Iᵥ, short circuit current.
Table 3  Histological score in relation to the status of the terminal ileum

<table>
<thead>
<tr>
<th></th>
<th>PDAI histology score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>Ileum prior colectomy</td>
<td>4.2 (1.1)</td>
</tr>
<tr>
<td>Deviation</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>Intact pouch</td>
<td>2.1 (0.9)</td>
</tr>
<tr>
<td>Pouchitis</td>
<td>5.2 (1.4)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

It has been hypothesised that pouchitis represents a clinical remanifestation of UC in the ileal pouch. As only little is known of the aetiology of UC, this hypothesis was based mainly on the similarity of pathophysiological features in both conditions, even if therapy was different. Whereas UC responds mainly to immunosuppressive drugs, firstline medication in pouchitis is the antibiotic metronidazole. Therefore, in the present study we tried to characterise epithelial transport and barrier function of the ileum after IPAA in patients with UC and to compare functional changes during pouchitis with inflamed UC mucosa.

**Barrier function**

To study epithelial barrier function in pouchitis, we measured electrical resistance as an (reciprocal) indicator of the permeability of small ions, and mannitol fluxes as an indicator of the paracellular “porosity” of larger molecules. Transport function was examined by measuring rheogenic Cl⁻ secretion and Na⁺-glucose cotransport.

**Porosity**

Our results did not show any significant differences in active transport or in parameters of permeability for pouchitis compared with the terminal ileum in UC or when transformed to a neorectum. These findings are in contrast with those of Merrett and colleagues who found increased porosity for ⁵¹Cr-EDTA in pouchitis compared with healthy pouches. In their study ⁵¹Cr-EDTA was administered into the ileal pouch or rectum and urinary recovery over 24 hours was taken as an indicator of permeability. Also, histological analysis of pouch biopsy specimens was performed. A negative correlation was found between barrier function and colonic metaplasia (villous height) and mucin type (sulphomucin). Merrett et al also demonstrated increased permeability for ⁵¹Cr-EDTA for the deviation group, which is in agreement with our results, at least for mannitol flux.

The different results concerning pouchitis may be due to different grades of pouchitis in the two studies. Another explanation may be differences in the methods used (⁵¹Cr-EDTA versus mannitol fluxes and alternating current impedance analysis). Analysis of barrier function allows examination of permeability of a constant surface area and a defined locus inside the pouch whereas in vivo absorption tests have no defined surface and an uncertain locus of absorption.

**Ion permeability**

In a previous study from our group, ion permeability was investigated in colectomised rats with an ileoanal pouch. We found that the epithelial barrier was not disturbed in the non-inflamed ileal pouch.

In the present study, we observed increased subepithelial resistance in the ileum of UC, intact pouch, and in pouchitis. We interpret this as the result of subepithelial tissue proliferation due to chronic inflammation of the terminal ileum. Similar findings were obtained in the ileal pouch of the rat. In view of adaptive changes, results of the blind loop formation in rat jejunum may be important. Here, subepithelial resistance increased together with reduced villus height. Another aspect was described by Garcia-Armengol and colleagues who examined chronologically mucosal changes and transepithelial potential differences. They found adaptive changes in the ileoanal pouch similar to those observed in the rectum at follow up, together with villus atrophy and lower potential differences in pouchitis.

In the human colon epithelial resistance is higher than in the terminal ileum. The epithelial resistances of intact pouches are comparable with those measured in non-inflamed tissue. In this context the findings in the hyper-regeneratively transformed coeliac sprue mucosa may be important. In healthy jejunum, epithelial resistance was 20 Ω×cm⁻¹ and although this control value is apparently low, epithelial resistance was further decreased in coeliac disease to a
value as low as 9 Ω·cm². This means that there is still room for a further deterioration in epithelial resistance.

The normal terminal ileum is not an “intermediate tight” epithelium like the colon but a “leaky” epithelium which cannot establish steep osmotic gradients and thus is unable to produce formed faeces. We found that the terminal ileum preserved epithelial resistance after pouch formation which also did not decrease during pouchitis. This means on the one hand that no functional adaptation of the “tightness” of the epithelium has occurred after pouch formation and on the other hand that epithelial barrier function is not impaired in pouchitis. As there were no large changes in epithelial resistances and it has been shown that resistance correlates logarithmically with tight junction strand count, we did not perform frozen fracture electron microscopy analysis.12

Transport function
Epithelial transport function was characterised by measuring active electroneutral chloride secretion and Na−-glucose cotransport.

Electrogenic chloride secretion
To assess the maximum transport rate for this transport system, the mucosa was stimulated by simultaneous addition of theophylline and prostaglandin E₁. In all five groups prior to and after ileoanal pouch formation, the transport function of the terminal ileum followed Michaelis-Menten kinetics and was reversible by serosal addition of bumetanide. This behaviour of the intestine is due to active electroneutral chloride secretion, as shown previously.13 15

This secondary active transport mechanism includes a Na−-K+−2Cl− cotransporter in the basolateral membrane of the enterocytes and a Cl− channel in the apical membrane. Our results indicate that there are two conditions for the terminal ileum after pouch formation with the highest decrease in electroneutral chloride secretion. These are the ileum during UC and after development of pouchitis. In both cases deterioration is explained by inflammation of the terminal ileum on the one hand, which is inflamed by backwash ileitis, and of the pouch on the other hand by idiopathic pouchitis.

Na−-glucose cotransport
Na+-glucose cotransport is quantitatively the most important absorptive ion transport system of the small intestine. This transport was characterised by measuring the increase in I⁶⁻ after gradual addition of 3-o-methyl-glucose to the bathing solution. 3-o-methyl glucose was chosen because it is transported but not metabolised.16 Michaelis-Menten saturation kinetics arise from the rate limiting Na−-glucose cotransport system in the apical membrane.17 During pouchitis, deviation, and in the terminal ileum during UC, Na+-glucose cotransport decreased compared with the intact pouch.

From these results we conclude that impairment of Na+-glucose cotransport becomes significant during pouchitis with bacterial overgrowth and may further increase stool volume in these patients leading to an increase in daily bowel movements.12

Comparison with ulcerative colitis
It was postulated that pouchitis is a remanifestation of UC in the ileum.9 Whereas transport function of the ileoanal pouch was reduced in pouchitis (versus intact pouch and control) for both sodium absorption and chloride secretion, the mucosa in UC did not exhibit any differences in electroneutral chloride secretion compared with controls. This may be due to differences between the small and large intestine or different degrees of inflammation in both conditions, but could also indicate two different types of pathogenicity. Mucosal barrier function was decreased in UC by >80% compared with controls.31 This is in agreement with the findings in ileoanal pouch where the epithelial barrier and porosity remained unchanged. Thus the hypothesis that pouchitis is a remanifestation of UC may not be completely valid.

In conclusion, this is the first study to analyse changes in transport function and permeability after ileoanal pouch formation under various conditions using an electrophysiological in vitro set up. In contrast with the study by Merret and colleagues12 we did not observe loss of barrier function during pouchitis. Additionally, examination of transport function revealed a dramatic decrease in electroneutral chloride secretion and Na−-glucose cotransport of ileal pouch mucosa during pouchitis.

REFERENCES

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Gut 2002 50: 821-826
doi: 10.1136/gut.50.6.821

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