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CAPSULE ENDOSCOPY IN THE DIAGNOSIS OF SMALL BOWEL DISEASE

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To Anders, Carolina and Ellinor

ABSTRACT

Capsule endoscopy (CE) is a method for examining the small bowel by means of an ingested encapsulated video camera, propelled by peristalsis, to continuously take images during its passage through the gastrointestinal tract. The method has been in clinical use in Sweden since 2002 and is considered user-friendly and well tolerable by patients. CE is used to diagnose obscure small-bowel bleeding, Crohn's disease (CD) and suspected small-bowel tumors. It is known for having a high sensitivity but a lower specificity.

In **study I** CE was performed in 18 patients with chronic intestinal dysmotility (CID), in which a high frequency of mucosal breaks (89%) was observed. There were signs of motility disturbances but the small-bowel transit time did not differ significantly between the two types of CID or to a control group. This was the first study to use CE in CID patients. CE was shown to be feasible for the examination of small bowel mucosa in patients with CID.

When CE is used to find a bleeding source in the small bowel, the most common finding are vascular malformations; angioectasias. These can also be found in non-bleeding patients but what triggers bleeding in some patients is not fully understood. In **study II** a group of 25 patients with bleeding from gastrointestinal angioectasias were tested for bleeding disorders with special focus on acquired von Willebrand syndrome (AVWS), a condition previously identified as a possible explanation for bleeding. Compared to a control group, no significant differences between groups were found in coagulation parameters, bleeding time or von Willebrand multimer levels. These results did not support the need for routine bleeding tests in cases of bleeding from angioectasias and do not demonstrate an overall increased risk of AVWS among these patients.

Inflammatory lesions in the small bowel showed by CE may be due to CD but also to other conditions. Since biopsies from the small bowel might be difficult to obtain the relevance of the lesions may remain unclear. In **study III** 30 patients with small bowel lesions were tested for inflammatory markers in blood (CRP) and faeces (calprotectin). Harvey-Bradshaw Index (HBI) was used to grade patient symptoms. The patients were followed up after nine months with a second capsule endoscopy, CRP, calprotectin and HBI. A significant correlation was found between endoscopic inflammation and calprotectin that persisted over time. A correlation between endoscopic inflammation and CRP was found at inclusion but did not persist at follow up. Symptoms did not correlate with endoscopic findings of inflammation at any time.

Study IV aimed to evaluate complications of capsule endoscopy, specifically incomplete examinations and capsule retention and to determine the risk factors for these. In this consecutive study 2300 CE examinations - performed at four different hospitals in Stockholm, Sweden from 2003 to 2009 - were included. The frequency of incomplete examinations was 20%. Older age, male gender and suspected or known CD were risk factors for an incomplete examination. Capsule retention occurred in 1.3%. Risk factors for capsule retention were known CD and a suspected tumor. CE was concluded to be an overall safe procedure, although obstructive symptoms and serious complications due to capsule retention can be found in large patient series.

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- I. **Höög CM**, Lindberg G, Sjöqvist U.
Findings in patients with chronic intestinal dysmotility investigated by capsule endoscopy.
BMC Gastroenterol. 2007 Jul 18;7:29.
- II. **Höög CM**, Broström O, Lindahl TL, Hillarp A, Lärfars G, Sjöqvist U.
Bleeding from gastrointestinal angioectasias is not related to bleeding disorders - a case control study.
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- III. **Höög CM**, Bark LÅ, Broström O, Sjöqvist U.
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- IV. **Höög CM**, Bark LÅ, Arkani J, Gorsetman J, Broström O, Sjöqvist U.
Capsule retentions and incomplete capsule endoscopy examinations: an analysis of 2300 examinations.
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CONTENTS

1	Introduction.....	1
2	Background.....	2
2.1	The small bowel and how to examine it	2
2.2	Capsule endoscopy	2
2.2.1	The process of capsule endoscopy	3
2.2.2	Indications for capsule endoscopy	3
2.3	Chronic intestinal dysmotility	4
2.3.1	Can CE find new clues to CID?	4
2.4	Angioectasias – a common reason for OGIB.....	4
2.4.1	AVWS - an explanation for bleeding from angioectasias?.....	4
2.5	Crohn’s disease	6
2.5.1	Diagnosing Crohn’s disease in the small bowel	6
2.6	Capsule retention and incomplete examinations.....	8
3	Aims	9
3.1	General aim	9
3.2	Specific aims	9
4	Methods	10
4.1	Capsule endoscopy.....	10
4.1.1	Preparation and procedure of capsule endoscopy	10
4.1.2	Viewing.....	10
4.2	Study I.....	10
4.3	Study II.....	11
4.3.1	The study group and inclusion criterias	11
4.3.2	The control group.....	11
4.3.3	Exclusion criterias.....	11
4.3.4	Laboratory testing	11
4.4	Study III	12
4.4.1	Lewis score	12
4.4.2	Harvey Bradshaw index, CRP and calprotectin.....	12
4.4.3	Inclusion criteria.....	12
4.4.4	Exclusion criteria	12
4.4.5	Study procedure	13
4.5	Study IV	13
4.5.1	Study centers	13
4.5.2	Indications for CE	13
4.5.3	Capsule retention.....	14
4.6	Statistics	14
5	Results.....	15
5.1	Study I.....	15
5.1.1	Frequency of incomplete CE.....	15
5.1.2	Median transit times.....	15
5.1.3	View	15
5.1.4	Mucosal breaks	15
5.2	Study II.....	17
5.3	Study III	18
5.3.1	Correlation - CE findings, inflammatory parameters and symptoms .	18
5.3.2	Did correlation remain at follow up?	20
5.3.3	Correlation to histopathological diagnosis.....	20
5.4	Study IV	22

5.4.1	Incomplete Examinations.....	22
5.4.2	Capsule Retentions.....	22
6	Discussion.....	25
6.1	CE at CID.....	25
6.2	Bleeding from angioectasias – due to a bleeding disorder?.....	26
6.3	CE findings suspicious for CD.....	27
6.4	Six years of CE experience in Stockholm.....	28
7	Future perspectives.....	29
8	Conclusions of the thesis.....	30
9	Populärvetenskaplig sammanfattning.....	31
9.1	Studie I: Falskt tarmvred.....	31
9.2	Studie II: Blödning från kärlförändringar.....	31
9.3	Studie III: Crohns sjukdom.....	32
9.4	Studie IV: Utvärdering av 2300 kapselundersökningar.....	32
10	Acknowledgements.....	33
11	References.....	35
12	Original papers.....	40

LIST OF ABBREVIATIONS

CE	Capsule endoscopy
GI	Gastrointestinal
CID	Chronic intestinal dysmotility
CD	Crohn's disease
OGIB	Obscure gastrointestinal bleeding
AVWS	Acquired von Willebrand syndrome
NSAID	Non steroid anti-inflammatory drug
LS	Lewis score
DAE	Device assisted enteroscopy
VW	von Willebrand
VWF	von Willebrand factor
HBI	Harvey-Bradshaw index
CRP	C-reactive protein

1 INTRODUCTION

The science of gastroenterology has developed significantly over the last 30 years. Discoveries like *Helicobacter pylori*, medicines against inflammatory bowel disease, laparoscopic surgical techniques and advanced imaging techniques have changed both our perception and our management of gastroenterological diseases.

The developments so far and to proceed on this track are of great importance since gastroenterological disease still is a common cause of illness in our society. The prevalence of inflammatory bowel disease in Sweden is approximately 0.5-1% and the incidence is increasing ¹⁻⁴. Colonic cancer is the most common type of gastrointestinal malignancy in Sweden with an incidence of approximately 4000 new cases per year ⁵. Every tenth visit to a general practitioner concerns a gastrointestinal disease ⁶.

Capsule endoscopy is one of the new imaging techniques that might contribute to further progress in the field of gastroenterology.

2 BACKGROUND

2.1 THE SMALL BOWEL AND HOW TO EXAMINE IT

The small bowel has a length of 4-5 meters and is thus by far, the longest portion of the gastrointestinal (GI) tract. The primary function of the small bowel is for digestion of the food and absorption of nutrients and minerals in the food. It also plays an important immunological role.

Because of its position in the middle of the GI tract, the small bowel is difficult to reach and to examine endoscopically. During the twentieth century endoscopic techniques were developed providing good visualization of the upper and lower GI systems including duodenum and terminal ileum. For examination of the deeper parts of the small intestine: middle and distal jejunum and ileum, radiology has remained as the only non-invasive technique for visualization. Although radiology has improved enormously during the last decade and computer tomography and magnetic resonance imaging have become increasingly available they still cannot provide a photographic image of the small intestinal mucosa. Difficulties in reaching the small bowel are probably a reason for why diseases in this area are difficult to define and diagnose.

2.2 CAPSULE ENDOSCOPY

Capsule endoscopy (CE) was introduced 2000 by Iddan et. al ⁷. CE is an ingestible capsule camera [figure 1] that takes photographs during its passage throughout the gastrointestinal tract ⁸.

For the first time it was possible to visualize the entire small bowel mucosa *in vivo*. The introduction of CE has revolutionised small bowel imaging and has been described as a paradigm shift ⁹⁻¹¹. The first capsule was manufactured by Given Imaging. It consisted of a lens, light source, imager, wireless transmitter and battery, and measured 11x26 mm. Newer models from Given Imaging and later on other manufacturers are basically similar but provides better resolution, faster image acquisition and longer battery times. In addition the software and recording equipment have improved.

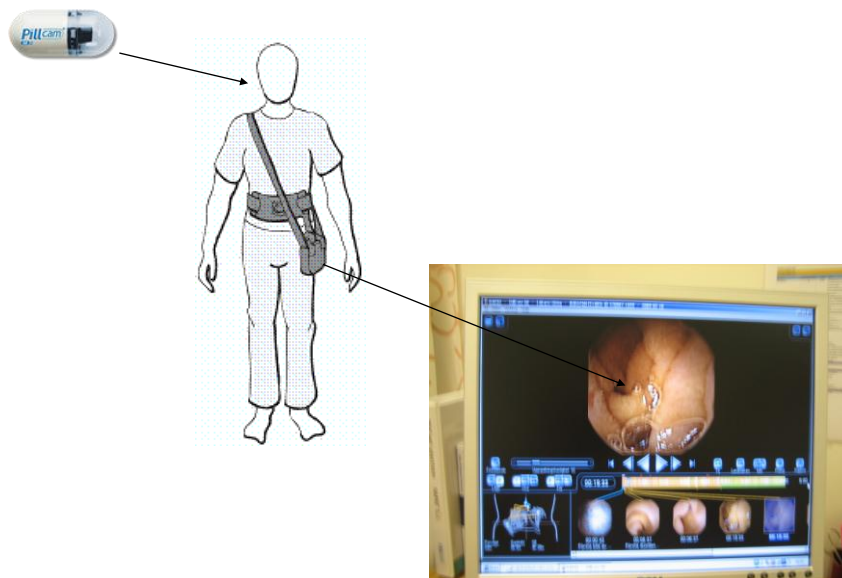


[1] Endoscopy capsules from the three different manufactures available in Sweden 2013.

2.2.1 The process of capsule endoscopy

Preparation for CE is usually a clear liquid diet the day prior to the examination. After an overnight fast, the capsule is ingested with two glasses of water. Sometimes a bowel preparation is also given^{12, 13} but its usefulness is a matter of debate^{14, 15}.

Recording devices are attached to the abdomen and worn by the patient during the entire examination. The images are directly transmitted to the recorder. The capsule takes between 2 and 35 images per second depending on type and chosen mode. The examination is completed in 8-11 hours usually when the battery wears out or the capsule is excreted from the body. The capsule is propelled by intestinal peristalsis, is disposable and excreted naturally by the stool. After the examination the recording device is returned to the endoscopy unit, all pictures are loaded from the recorder onto a computer and can then be read one by one or on film [figure 2].



[2] The capsule is ingested and is propelled through the GI tract by peristalsis. Images are sent continuously to the recording equipment. After completion of the examination the images are loaded onto a computer for reading.

2.2.2 Indications for capsule endoscopy

CE was first approved for identifying small bowel bleeding source and was soon shown to be very useful¹⁶. It was shown that CE was far more sensitive in finding a bleeding source than the traditional methods such as; push-enteroscopy, small bowel follow through with enteroclysis and computed tomography¹⁷. Although computed tomography and magnetic resonance imaging have improved rapidly during recent years, CE still stands out as a more sensitive alternative¹⁸⁻²⁰ and is recommended as the first line method for the diagnosis of obscure small bowel bleeding^{11, 21, 22}.

Crohn's disease (CD) in the small bowel is another indication for CE^{23, 24} and has shown to be more sensitive than its predecessors²⁵⁻²⁷. Other indications for CE include suspected small bowel tumors²⁸ and complications of celiac disorders; ulcerative jejunoileitis and lymphoma²⁹⁻³¹.

Contraindications for CE are swallowing disorders, pregnancy, implanted intracardial defibrillators and known bowel obstruction¹⁴. The suspicion for bowel obstruction is a relative contraindication and must be treated with special consideration. This topic is discussed later on.

Hence CE has become a popular diagnostic tool, known not only for its high sensitivity but also being user-friendly and well-tolerated by the patients³².

2.3 CHRONIC INTESTINAL DYSMOTILITY

The possibility of visualizing the entire small intestine *in vivo* increases the means to find new clues to diseases that has remained incompletely understood.

Chronic intestinal dysmotility (CID) is a syndrome characterized by symptoms and signs of intestinal obstruction in the absence of a mechanical blockage³³. It is also known as “pseudo-obstruction”. CID is caused by abnormalities in the intestinal smooth muscle layer or the myenteric plexus, usually selectively affecting one of them. The underlying pathology in CID is thus believed to comprise two major types: myopathic and neuropathic disorders, although they tend to present with similar clinical manifestations³⁴.

Symptoms of CID include abdominal pain, vomiting and diarrhea. CID is currently diagnosed by small bowel manometry and full thickness intestinal biopsy³³.

2.3.1 Can CE find new clues to CID?

Previously mucosal defects were not expected to be seen in the small bowel of patients suffering from CID. On the other hand the mucosa had not been completely visualized *in vivo* before, due to the difficulties in endoscopic accessibility. Capsule endoscopy presented the possibility to determine if this assumption was true. Moreover since the capsule is propelled by intestinal peristalsis a difference in the capsule movement between CID patients and a control group, might be possible to detect.

2.4 ANGIOECTASIAS – A COMMON REASON FOR OGIB

Obscure gastrointestinal bleeding (OGIB) is the most common indication for capsule endoscopy^{35,36}. One of the most common findings, that possibly explain the bleeding, are vascular malformations – angioectasias^{16,36} (also known as angiodysplasia). Angioectasias in the gastrointestinal tract is seen as a sharp red flat 3-7 mm lesion in the mucosa [figure 3, 4] and can be found in up to 3% of the population³⁷. They can be found throughout the whole GI tract but are most common in the right colon³⁸. Angioectasias are typically asymptomatic but may sometimes cause severe bleeding. The reasons for why some patients bleed from their angioectasias and some do not, are not fully understood but it has been reported that it may be explained by an acquired von Willebrand syndrome (AVWS)³⁹.

2.4.1 AVWS - an explanation for bleeding from angioectasias?

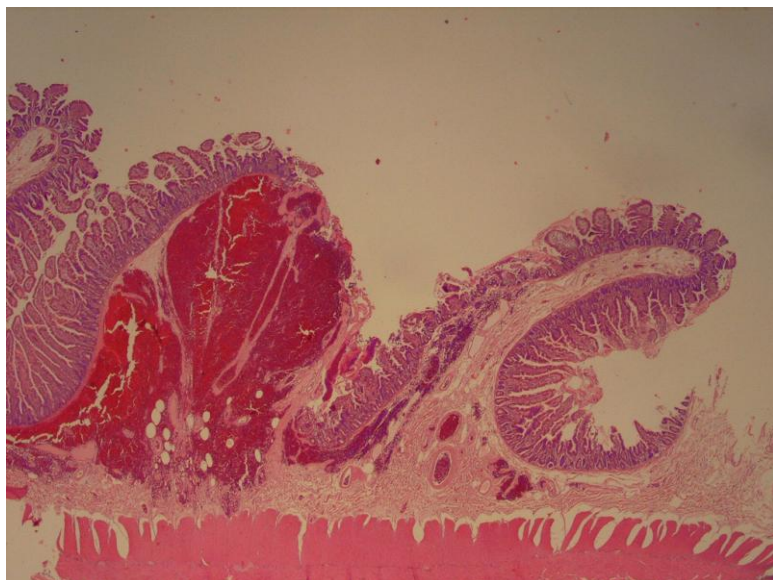
AVWS is a condition with similar laboratory findings as congenital von Willebrand disease where a selective loss of large von Willebrand multimers is seen⁴⁰. One reason for this is that in AVWS, a proteolytic cleavage occurs in the changed blood flow in patients with a heart valvular disease, such as aortic stenosis⁴¹. The large multimers of von Willebrand are important in maintaining hemostasis under the conditions of increased wall shearing forces, with an increased blood flow speed close to the vessel wall. Similar conditions are found in

the blood flow of angioectasias. AVWS could then be suspected to be associated with bleeding from angioectasias.

This correlation was observed in a small sample size study⁴² where eight out of nine patients with bleeding from angioectasias were also found to have AVWS. Should we then test all patients with bleeding from angioectasias for AVWS? To answer this question there is need for testing of a larger sample size and also testing if other bleeding deficiencies can be found.



[3] Angioectasia in the small bowel, imaged by CE.



[4] Angioectasias, microscopical image showing enlarged submucosal blood vessels.

2.5 CROHN'S DISEASE

Crohn's disease (CD) is an inflammatory bowel disorder that is considered to be of autoimmune genesis^{43, 44}. CD can occur in the entire gastrointestinal tract and typically causes inflammation and ulcers in the mucosa. In 45% of the patients the small bowel is involved [figure 5, 6] at the time of diagnosis^{2, 45}.

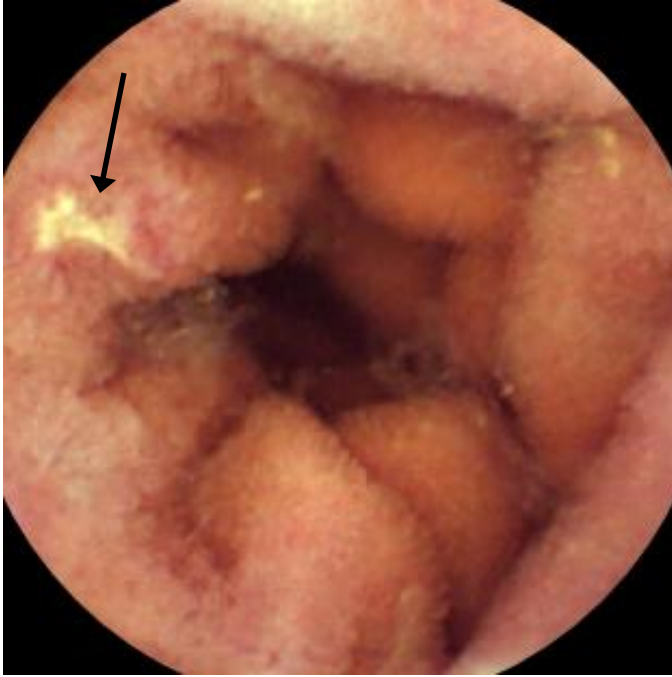
Crohn's disease is a chronic disorder affecting primarily young people although the disease can occur in all ages². CD is characterized by alternating periods of relapse and remission⁴⁶. Symptoms include abdominal pain, fever, diarrhea and intestinal bleeding⁴⁷. CD is a clinical diagnosis that integrates history and physical findings with objective data from imaging and laboratory studies, including histopathology, and should neither be based nor excluded on any one variable or result^{43, 48}.

2.5.1 Diagnosing Crohn's disease in the small bowel

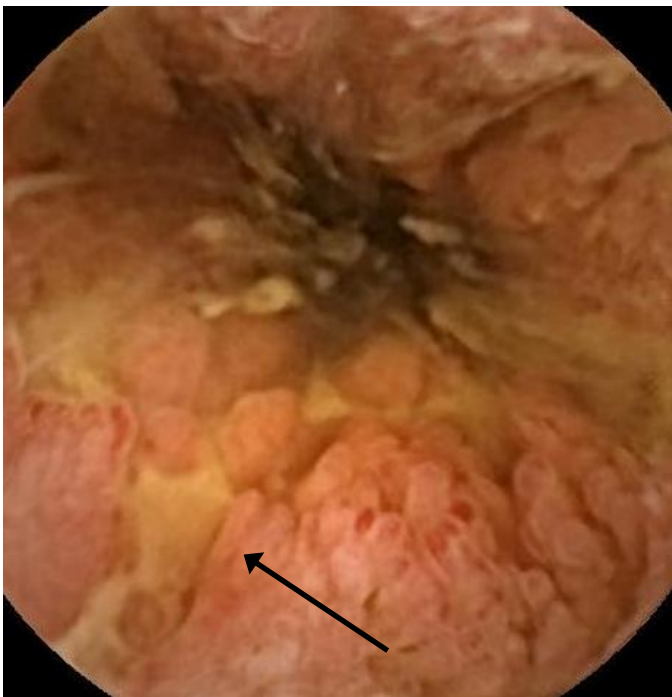
A major disadvantage of CE is its limited specificity^{21, 27, 49} which can cause over-diagnosis especially when interpreted by beginners. Ulcers and inflammatory areas (villous oedema) resembles the look of CD but could be due to other pathology such as use of non-steroid inflammatory drugs (NSAID)⁵⁰ or infectious diseases (e.g. Yersinia⁵¹ or tuberculosis⁵²). Therefore there is a need for confirming the nature of the found lesions. CE lacks the ability to take biopsies for histopathological analysis.

The introduction of deep enteroscopy by means of device assisted enteroscopy (DAE)^{53, 54} resulted in improvements in the diagnosis of CD. DAE makes it possible to reach also deeper parts of the small bowel with an endoscope provided with a working-channel for the purposes of biopsy and intervention. However DAE is time- and resource consuming and do not always succeed in reaching the deepest part of the small bowel⁵⁵. Moreover the results of biopsy analysis can be inconclusive due to sampling error or the unpredictable relapsing-remitting course of the disease⁴⁹.

Since the diagnose of CD is based on a combination of clinical and laboratory findings including endoscopy^{43, 49} we need to learn more about the significance of inflammatory lesions seen on CE. A score for grading inflammatory lesions seen by CE, the Lewis score (LS)⁵⁶, has been developed and validated⁵⁷. A correlation between LS and fecal calprotectin, which is a marker of inflammatory bowel disease^{58, 59}, has been shown⁶⁰. Another study demonstrated a sensitivity and specificity of 93 and 84%, respectively when inflammatory lesions were found on CE in the small bowel in patients with suspected CD⁴⁹. However the sensitivity for fecal calprotectin to detect small bowel CD has been reported to only 59%⁶¹. Thus there is need for more robust evidence for the correlation between visualized inflammation in the small bowel and inflammatory parameters as well as clinical symptoms.



[5] Single ulcer due to CD in the small bowel, image by CE.



[6] Crohn's disease in the small bowel, severe inflammation, image by CE.
Note the yellow coloured ulcers interspersed with the inflamed villi.

2.6 CAPSULE RETENTION AND INCOMPLETE EXAMINATIONS

Another concern of CE is the risk of capsule retention⁶² - when the capsule is unable to pass a stricturing lesion [figure 7] in the bowel and remains there. This complication is extremely rare in patients examined for occult GI bleeding³⁵ while a high risk has been reported in patients with known obstructive CD⁶³. If the capsule does not reach the cecum during recording time the examination is considered to be incomplete and important information can be missed, in some studies this has been reported in one out of five examinations³⁶.

In Sweden CE has been performed since 2002, in Stockholm since 2003 and by the close of 2009 more than 2000 examinations had been performed there. A new method requires validation in different settings and before proceeding with this number of examinations a validation is needed, especially with focus on risks and outcomes of examinations resulting in permanent capsule retention. The question of how to consider incomplete examinations also needs to be addressed. The Stockholm experience offers a good opportunity for this purpose.



[7] Stricture in the small bowel due to previous radiation, image by CE. The capsule is pushed against the stricture thus making the mucosa to whitening.

3 AIMS

3.1 GENERAL AIM

The aim of this thesis is to increase the knowledge and critically evaluate the use of capsule endoscopy and its capability to diagnose small bowel disease.

3.2 SPECIFIC AIMS

1. To evaluate the small bowel mucosa of patients with CID (study I).
2. To determine if CE, by evaluating small bowel transit, can differentiate between the two types of CID and from a control group (study I).
3. To determine whether bleeding from gastrointestinal angioectasias, is caused by AVWS or other bleeding disorders (study II).
4. To determine whether there is a correlation between CE findings of small bowel inflammation and inflammatory parameters in blood and faeces (study III).
5. To investigate if there is a correlation between CE findings of small bowel inflammation and symptoms (study III).
6. To evaluate CE with regards to incomplete examinations and capsule retentions in a large unselected population by including all CE performed in Stockholm county during six years (study IV).
7. To find risk factors for incomplete examination and capsule retention (study IV).
8. To characterize the clinical outcomes of patients with capsule retention (study IV).

4 METHODS

4.1 CAPSULE ENDOSCOPY

In study I and II, the Pillcam-capsule from Given Imaging (Yoqneam, Isreal) was used. The later version; Pillcam SB2 was used in study III and IV and the MiroCam capsule (Intromedic, Seoul, Korea) was also used in these studies. In study IV the Olympus capsule (Olympus, Tokyo, Japan) was also used in a subset of cases.

4.1.1 Preparation and procedure of capsule endoscopy

The patients were instructed to consume only liquid food on the day before and no oral intake at all from midnight the night before examination. No bowel preparation was given in general in studies I, II and IV. In study III one of the participating centres gave 2 Liters of polyethylene glycole to patients with known Crohn's disease. This regime was based on the experience from study IV where a subanalysis showed an impaired view during capsule endoscopy in this subgroup of patients.

The patients swallowed the capsule along with 250-500 ml of water. After two hours clear liquid intake was recommended and a regular diet after 4 hours. The patients were also encouraged to move around during the examination e.g. walking, in order to stimulate the intestinal peristalsis.

If the capsule did not reach the cecum during the recording period, complete small intestinal passage was controlled by fluoroscopy, which was performed within a couple of weeks after the CE examination.

In a few patients in which slow gastric transit was highly likely (diabetics, inward-patients, those on opioids and those with a history of gastric retention during CE) a real time viewer was used 1 hour after ingesting the capsule. If gastric mucosa was visualized at that point, a gastroscopy was performed, and the capsule was manually placed in the duodenum using a Roth-net.

4.1.2 Viewing

The CE examinations were viewed and interpreted by gastroenterologists with experience of endoscopy at the tertiary referral centres participating in the studies. One examination took approximately 45 minutes to view. In study I and III all videos were viewed and interpreted by two readers and only findings that both agreed to be significant were recorded.

4.2 STUDY I

Eighteen patients with CID underwent CE for the purpose of this study. The patients had a well documented motility disorder. Their diagnosis was based upon clinical features, x-ray findings, small-bowel manometry and intestinal full thickness biopsy. Six of them had myopathic, 11 had neuropathic and one had indeterminate CID. Their ages ranged between 35–85 (median 54) years and 12 were females (67%). Including intestinal full thickness biopsy the patients had previously undergone abdominal surgical interventions 1–10 (median 2) times. Surgery had been performed for different indications including cholecystectomy, appendectomy, gynecological interventions and bowel resections aimed to treat the underlying motility disorder.

No drugs that might interfere with motility were allowed for 48 hours before examination. The CE readers were blinded for the type of CID the patients had as well as for all other clinical information.

In order to evaluate small bowel transit in the study group, a control group was used. The control group consisted of 36, randomly selected, age and gender matched patients who previously had undergone capsule endoscopy due to occult gastrointestinal bleeding.

4.3 STUDY II

4.3.1 The study group and inclusion criterias

Twenty-five patients with a prior history of gastrointestinal bleeding resulting in anemia due to angioectasias in the gastrointestinal tract were identified and retrospectively enrolled in the study. The mean age was 72, range 35-86 years and 15 patients were female (60%). All study participants had previously undergone upper and lower endoscopies. Angioectasias were found in the upper GI tract in 7 patients, in the small intestine in 5 patients, in the lower GI tract in 7 patients and in multiple locations in 4 patients. Angioectasias found in the small intestine were diagnosed by means of CE. The diagnosis of angioectasia was based upon endoscopic findings of a flat bright reddish lesion of a typical appearance, measuring 3-10 mm. The angioectasias were considered to be the only source of bleeding in the study group.

4.3.2 The control group

The study group was compared to a retrospective control group consisting of 24 patients diagnosed with diverticulosis. The mean age of the control group was 73, range 60-86 years and 15 were females (62%). All patients in the control group had previously undergone upper and lower endoscopies without identification of angioectasias. The original indications for endoscopy included gastrointestinal bleeding, abdominal pain or diarrhoea.

4.3.3 Exclusion criterias

Exclusion criteria for both groups were as follows: malignancy, the use of warfarin during the bleeding episode, the absolute need for drugs affecting bleeding parameters, a known bleeding disorder, thrombocytopenia, kidney failure (serum creatinine greater than 150 mmol/L), alcoholic over-consumption and severe psychiatric illness. Patients enrolled were asked to leave blood tests on one occasion.

All drugs that might affect bleeding parameters were stopped two weeks before blood tests were performed.

4.3.4 Laboratory testing

Haemoglobin level, platelet count, serum creatinine and activated partial thromboplastin (APT) time were determined for all study participants. Bleeding time (according to Ivy) was tested utilising a Surgicutt™ device. For coagulation analysis, blood was collected in Vacutainer tubes containing 1/10 volume sodium citrate, with the plasma separated immediately after blood collection. Plasma was stored at -70°C until analysis. Factor VIII was measured with a chromogenic assay, prothrombin time with the reagent GHI-131, von Willebrand-antigen and von Willebrand-activity with reagents from Instrumentation Laboratory utilising an ACL Top (IL). These tests were performed at the coagulation laboratory of Linköping University Hospital.

The multimeric pattern of von Willebrand factor (VWF) in the plasma was analyzed by electrophoresis on 1.9% SeaKem HGT(P) agarose gel in the presence of sodium dodecyl sulphate followed by immunoblotting with antibodies against VWF⁶⁴. The multimeric distribution was thereafter quantitated using densitometric analysis with peaks 1 - 5 representing small, peaks 6 -10 intermediate and peaks above 10 large multimers as described by Budde et al⁶⁵. Analysis of VWF was performed at Malmö University Hospital. Blood sampling and bleeding-times were performed by one trained nurse in Södersjukhuset, Stockholm.

4.4 STUDY III

In this study 30 patients with inflammatory lesions in the small bowel diagnosed by CE were recruited. Median age was 37 (19-77) years and 12 patients were female (40%).

4.4.1 Lewis score

The capsule endoscopic findings of inflammation was graded using Lewis Score (LS)⁵⁶. The score assigns points for mucosal oedema, ulcers and strictures. Only the most affected tertiary portion of the small bowel is counted. A score less than 135 points are considered as normal or clinically insignificant, 135-790 is considered low graded inflammation and greater than 790 moderate to severe inflammation.

4.4.2 Harvey Bradshaw index, CRP and calprotectin

The Harvey Bradshaw index (HBI) is a validated symptom-based scale for grading of Crohn's disease activity with regards to severity of symptoms⁶⁶.

C-reactive protein (CRP) is known to correlate well with inflammatory activity of CD in the GI tract^{67,68} and was used to grade the inflammation in blood.

Calprotectin is a fecal marker that grades the level of CD inflammation⁵⁸ by measuring a protein released in the stool. A normal value is considered to be less than 50, but the levels vary on an individual basis. Elevated levels are found especially in inflammatory bowel diseases but can also be seen in patients with infection or neoplasia⁶⁹. However elevated levels can also be found in healthy persons⁷⁰. Calprotectin was used as the inflammatory parameter in stool samples, since it seemed to be the best alternative⁶¹.

4.4.3 Inclusion criteria

- Inflammatory lesions with a Lewis score of 135 or more diagnosed by CE.
- Known or suspected Crohn's disease.
- A recent colonoscopy ruling out active inflammatory bowel disease in the colon.

4.4.4 Exclusion criteria

- Regular use of NSAIDs
- Active inflammation in another part of the GI tract.
- Known or suspected small bowel stricture.

4.4.5 Study procedure

The patients were recruited after a CE examination with findings of inflammatory lesions with a Lewis score of at least 135. They were asked to fill in a questionnaire about symptoms and medication used. The questions were designed to match the HBI. Patients donated one blood sample for CRP and a stool test for calprotectin. Patients referred to CE by their gastroenterologist were referred back for follow-up with a decision of treatment and/or further investigations. Patients referred from their primary care physician were given an appointment with a gastroenterologist at the clinic. Decision of treatment and/or further investigations usually DAE, was based on the clinical presentation.

Regardless of therapy chosen, all the patients were asked to return for a new CE, after approximately 9 months. Then they also filled in a new questionnaire and repeated measurements of CRP and calprotectin. Patients diagnosed with a narrow stricture at the first CE instead underwent magnetic resonance imaging.

4.5 STUDY IV

This study was comprised of 2300 small-bowel CE examinations performed at 4 different hospitals in Stockholm, Sweden between June 2003 and December 2009. All CE studies performed in Stockholm County (population 2 million inhabitants), during this time period were included, which made the study conclusive.

4.5.1 Study centers

CE was first introduced in Stockholm at Södersjukhuset (Centre 1) in June 2003. The Given PillCam SB capsule endoscope was used, and 1473 (64%) of all investigations in the study were performed at this centre. Karolinska University Hospital (Centre 2) started CE examinations 4 years later (June 2007), used Olympus capsule system and performed 490 (21%) of the examinations. Ersta Hospital (Center 3) also started in June 2007, and at this hospital 302 (13%) CE examinations were performed. Danderyd Hospital (Center 4) started CE examinations in August 2009, using the MiroCam capsule device and had performed 35 (2%) examinations by the close of 2009.

All centres contributed data to the total number of CE examinations that were performed. Centres 1 and 2 contributed with data on age, gender, indications, view and findings for all patients receiving CE during the study period ($n = 1963$, 85% of the all CE examinations). Centres 3 and 4 contributed this data for all patients with an incomplete capsule examination.

4.5.2 Indications for CE

Indications for CE included obscure gastrointestinal bleeding (OGIB), known or suspected CD, suspected tumor and “other”. A tumor was suspected when a previous radiological examination, primarily computer tomography, demonstrated findings or when there was a clinical suspicion of malignancy, such as weight loss, unexplained fever, laboratory findings in combination with GI symptoms. “Other” indications included diarrhea, celiac disease and abdominal pain. All medical charts and records of the patients referred for CE were reviewed by a gastroenterologist. If the indication for the CE was bleeding, all patients must have had at least one normal gastroscopy and one normal colonoscopy at a concurrent time. In cases of suspected or known CD, contraindications such as symptoms of small bowel obstruction or known strictures were first ruled out. Radiological exclusion of strictures by means of enteroclysis, MRI, or CT was not required prior to CE.

4.5.3 Capsule retention

Capsule retention was defined as the capsule device remaining within the small intestine, as evidenced by radiologic examinations two weeks after the procedure, or found during abdominal surgery in an obstructed portion of the small intestine. Patients with a confirmed, indefinitely retained capsule were usually referred for surgery and in all cases were closely followed up. Prior to surgery radiologic studies were repeated. In a few cases the capsule had passed spontaneously, even after several months of retention, and these patients were then excluded from the capsule retention group.

Patients with definitive capsule retention are presented in detail in study IV.

4.6 STATISTICS

- Study I: Median values with ranges were used in the text. Kaplan-Meier plots and the log-rank test were used for the analysis of differences in small bowel transit times between the study groups and control group.
- Study II: Median values with range were used in the text. Non parametric statistics of mean values (Mann-Whitney-U test) were used for comparison between the study group and control group.
- Study III: Spearman's rank correlation coefficient was used to calculate the correlation between LS, CRP, HBI and calprotectin as well as to calculate correlation of difference between the parameters at the first and the second examination. This test was chosen because HBI partly is based on nominal data and because of skewed data with the presence of outliers. To compare means between patients with a biopsy verified diagnosis and those without, the Mann-Whitney U-test was used.
- Study IV: To identify risk factors for capsule retention and incomplete CE examination, a multivariable analysis using logistic regression was made. Pearson's chi-square tests were used for calculating the significance of differences between the two capsule systems Given and Olympus.

All calculations were made using SPSS Statistics software (IBM, Somers, USA). The level of significance was set at 0.05, two sided, for all analyses.

5 RESULTS

5.1 STUDY I

All patients underwent the examination without complications. None of them developed symptoms of intestinal obstruction during the examination and no one needed endoscopic or surgical capsule removal.

Three patients retained the capsule in the stomach (defined in this study as more than two hours in the stomach), one of them for the entire recording time. This patient underwent a new CE with endoscopic placement of the capsule in the duodenum and this capsule reached the cecum within the recording period. One patient had retention of the capsule in the oesophagus for 20 minutes.

5.1.1 Frequency of incomplete CE

The capsule reached the cecum during the eight-hour recording time in 11/18 (61%) patients. In patients with myopathic CID the capsule reached the cecum during the recording time in only 2/6 patients. In the control group the capsule reached the cecum in 29/36 (81%) patients. If the capsule did not reach the cecum during the recording time, the examination was considered as incomplete and the small bowel transit time was estimated to >400 minutes.

5.1.2 Median transit times

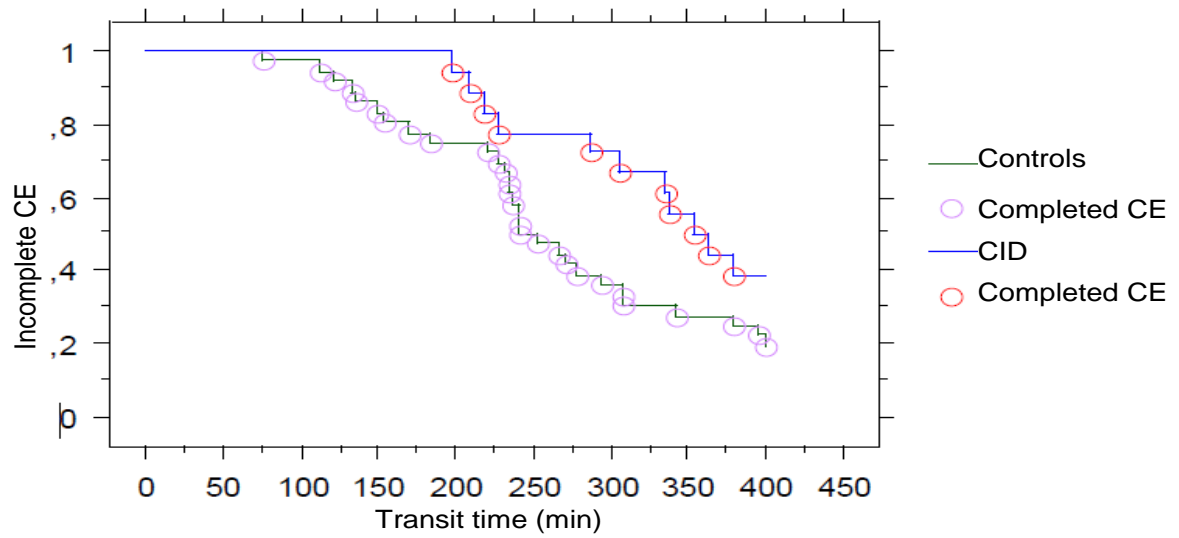
The median transit time in neuropathic CID was 305 (197 – >400) minutes whereas in myopathic CID the median transit time was >400 (219 – >400) minutes ($p=0.051$). In the whole study group median transit time was 346 (197 – >400) minutes, whereas in the control group it was 241 (75 – >400) minutes ($p=0.061$) [figure 8].

5.1.3 View

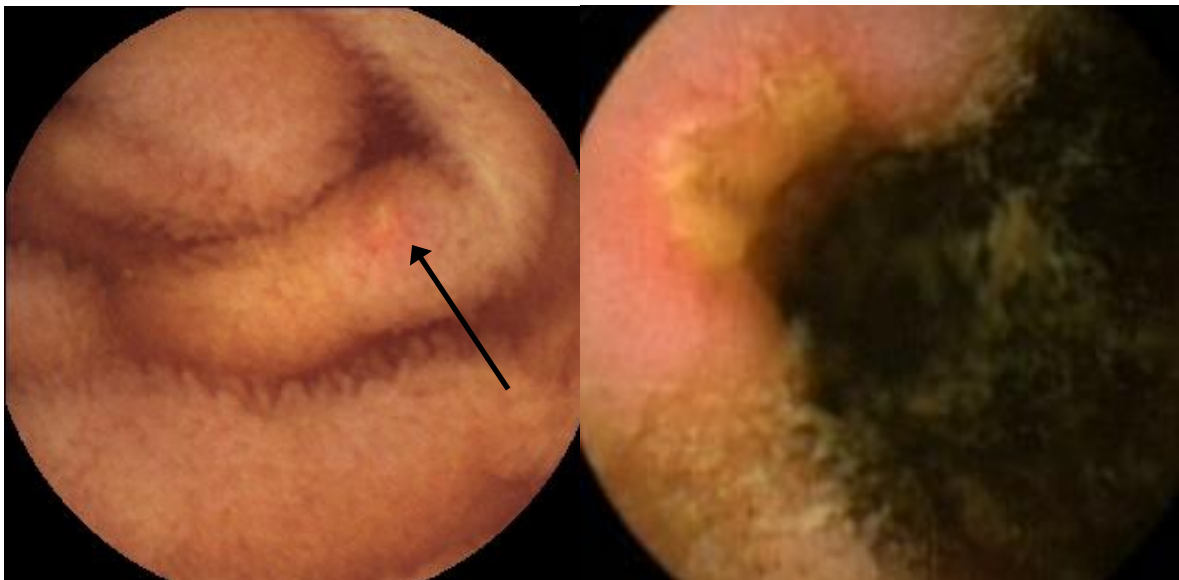
The view was considered clear with little or no intestinal content in only 10/18 (56%) patients. In cases where the view was reduced the reason was primarily due to large amounts of intestinal content. In the control group the view was considered clear in 30/36 (83%) patients.

5.1.4 Mucosal breaks

Mucosal breaks were found in 16/18 (89%) patients and in 7 patients there were multiple lesions (three or more). Mucosal breaks were classified into erosions and ulcerations. Findings defined as erosions included not only erythema but also some loss of mucosa and often a small fibrin clot could be seen [figure 9]. Ulcerations, on the other hand, were larger, deeper and covered with fibrin [figure 10]. Erosions were the dominating type of mucosal breaks observed.



[8] Kaplan-Meier plot of small bowel transit times in the study group (CID) and control group (controls).



[9] Erosion in the small bowel, image by capsule endoscopy (left).

[10] Ulcer in the small bowel, image by CE (right).

5.2 STUDY II

Two patients from the study group were excluded due to malignancies discovered during the study period. The remaining 23 patients were compared to the 24 patients in the control group.

Hemoglobin levels were significantly lower in the study group compared to the control group (median 129 vs 139, $p = 0.029$). There was no significant difference in any of the other parameters examined. The results are shown in Table 1.

Although the results of the study group did not significantly differ from those of the control group, 2 patients in the study group were found to have slightly depleted levels of the largest multimers of von Willebrand (both 20%, normal level 22-27%). Also in the study group, two patients had non measurable bleeding times (>900 seconds).

Table 1:

Parameter	Study group, mean (min-max)	Control group, mean (min-max)	Significance, P-value <0.05
Hemoglobin level, g/L	128 (97-151)	141 (113-169)	0.0294
Platelet count, $10^9/L$	262 (140-457)	265 (176-562)	NS
Creatinine, mmol/L	75 (56-136)	76 (62-112)	NS
C-reactive protein, mmol/L	<10 (<10 -25)	<10 (<10 -20)	NS
Protrombin time-INR	1.0 (0.9-1.2)	1.1 (0.9-1.2)	NS
APT-time, sec	35 (28-47)	34 (27-41)	NS
VW-antigen, kIU/L	1.47 (0.68-3.63)	1.50 (0.68-2.48)	NS
VW-activity, kIU/L	1.20 (0.70-3.39)	1.20 (0.69-2.23)	NS
Factor VIII, kIU/L	2.00 (1.01-3.84)	2.0 (0.99-2.52)	NS
Fibrinogen, g/L	3.9 (2.8-5.5)	3.9 (2.9-4.7)	NS
Large VW-multimer, %	28.4 (20.4-32.4)	29.9 (24.1-37.5)	NS
Bleeding time (Ivy), sec	Median* =270 (130-900)	Median* =250 (149-570)	NS

* =In this instance the median was used instead of mean as the value could not be measured above a certain level

5.3 STUDY III

All 30 patients completed the study except for one patient who was excluded for a second CE due to several narrow strictures found at the first CE. Instead a MRI was performed which only showed normal findings despite the known strictures.

The median, mean and range for the Lewis score (LS), HBI, CRP and calprotectin levels at inclusion (0) and at follow-up (1) are shown in table 2.

Table 2

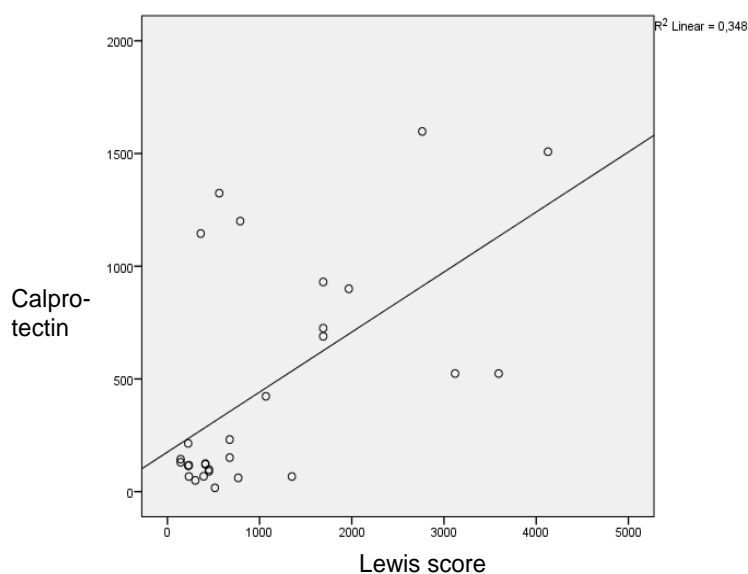
		LS 0	HBI 0	CRP 0	Calp 0	LS 1	HBI 1	CRP 1	Calp 1
<i>n</i>	Valid	30	30	30	29	29	30	30	28
	Missing	0	0	0	1	1	0	0	2
Mean		1050	5	9	461	478	4	9	215
Median		538	4	4	151	225	4	4	121
Range		135-3985	0-12	1-52	15-1581	0-3664	0-13	1-146	15-1058

5.3.1 Correlation - CE findings, inflammatory parameters and symptoms

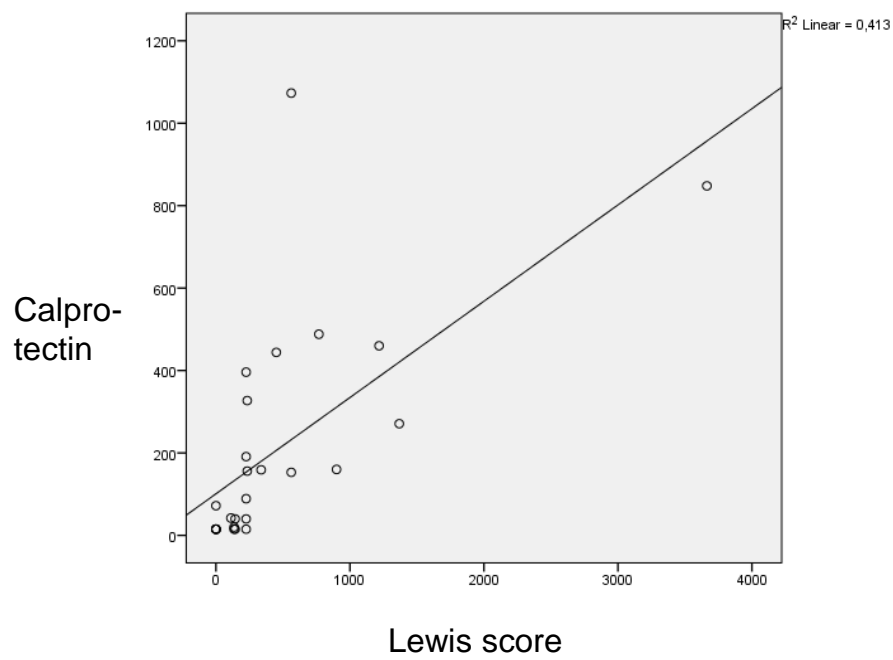
LS correlated with calprotectin both at inclusion ($p = 0.003$, $r = 0.54$) and follow up ($p < 0.001$, $r = 0.83$) [figure 11a+b].

LS correlated with CRP at inclusion ($p = 0.006$, $r = 0.49$) but not at follow up ($p = 0.11$, $r = 0.30$) [figure 12a+b].

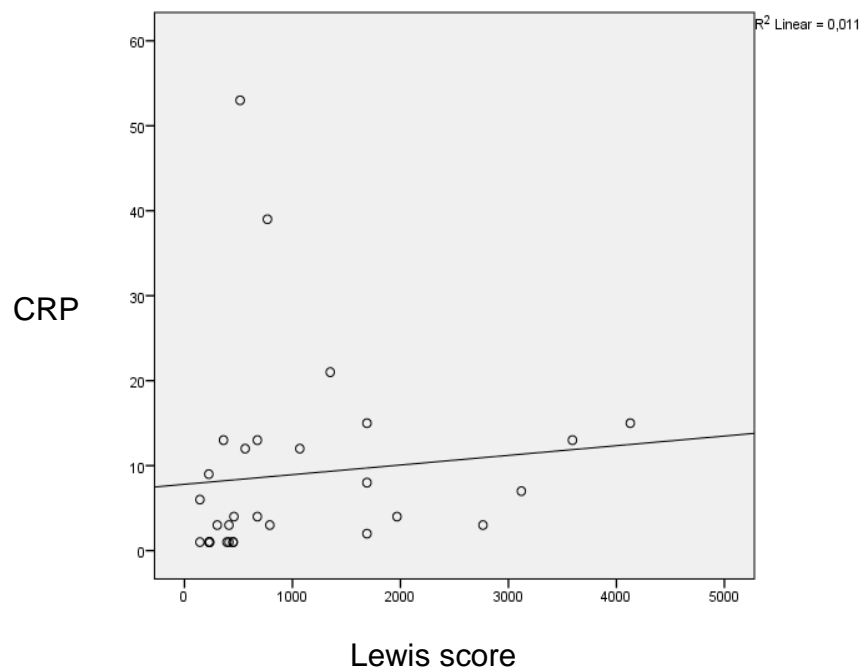
LS did not correlate with HBI at inclusion ($p = 0.211$, $r = 0.24$) or at follow up ($p = 0.98$, $r = -0.04$), figures not shown.



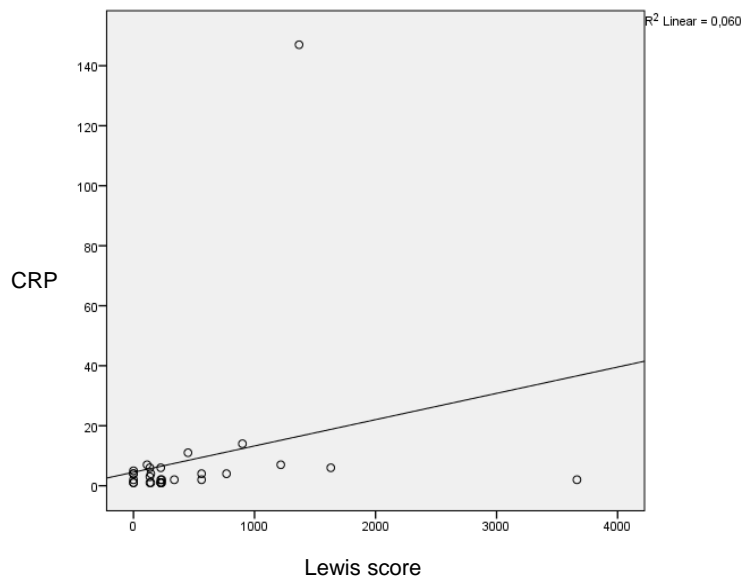
[11a] Lewis score and calprotectin levels at inclusion.



[11b] Lewis score and calprotectin levels at follow up.



[12a] Lewis score and CRP levels at inclusion.



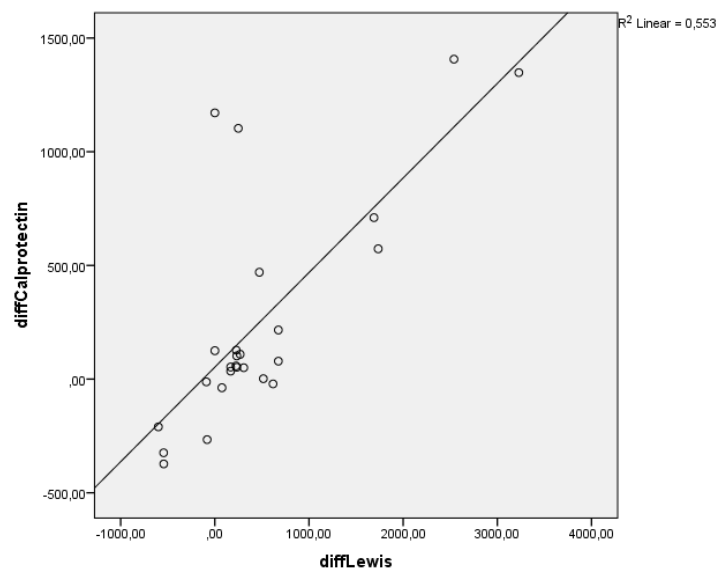
[12b] Lewis score and CRP levels at follow up.

5.3.2 Did correlation remain at follow up?

In order to determine if the correlation persisted over time and of varied disease activity, the difference between values at inclusion =0 and follow up =1 was calculated. The difference between LS (LS 0 – LS 1 =diff-LS) was correlated to the difference between calprotectin levels (calprotectin 0 – calprotectin 1 =diff-calprotectin), $p < 0.001$, $r = 0.65$, [figure 13]. Diff-LS did not correlate with diff-HBI ($p = 0.56$, $r = 0.11$) or diff-CRP ($p = 0.16$, $r = 0.26$).

5.3.3 Correlation to histopathologic diagnosis

CD was confirmed in 13 out of 30 patients by histopathologic diagnosis. The lesions in the other 17 patients were not reachable, not remaining at the time for endoscopy, or biopsy resulted in an inconclusive diagnosis. LS and calprotectin levels were significantly higher among patients with a histopathologic diagnosis of CD ($p = 0.026$ and $p = 0.012$, respectively) compared with patients without a conclusive histopathologic diagnosis.



5.4 STUDY IV

2300 CE examinations were performed in Stockholm County between June 2003 and December 2009. The overall indications for CE (known for all patients from Centres 1 and 2, $n = 1957$, 85% of all CE examinations) were:

- OGIB ($n = 1034$, 53%)
- suspected CD ($n = 577$, 29%)
- known CD ($n = 152$, 8%)
- suspected tumor ($n = 118$, 6%)
- others ($n = 78$, 4%)

The mean age was 51 years (range 2–99 years) and 57% were female ($n = 1117$). The diagnostic yield was 55%.

5.4.1 Incomplete Examinations.

463 (20%) examinations were incomplete, defined as the capsule failing to reach the cecum during the recording time. The mean age was 53 range 6–99 years and 53% were female. The diagnostic yield was 51% and the findings were:

- CD 22%
- slow gastric transit 14%
- vascular disease 8%
- suspected tumor 4%
- others 17%

5.4.1.1 Risk Factors for Incomplete Examination

The risk of incomplete examination was higher for male patients with an odds ratio of 1.34 (1.08–1.67, $p = 0.009$) and increased with age with an odds ratio of 1.02 per year (1.01–1.02, $p < 0.001$). The odds ratio for an incomplete examination was also significantly elevated for patients with both suspected and known CD, suspected tumor, and other indications compared to OGIB.

5.4.2 Capsule Retentions

Capsule retention occurred in 31 (1.3%) patients. The mean age was 51 range 14–81 years, and 47% were female. Diagnostic yield was 90% and the findings were:

- CD 48%
- tumor 19%
- stricture (non-CD) 13%
- erosions 6%
- on-going bleeding 3%
- normal findings 10%

5.4.2.1 Clinical outcome of patients with capsule retention

In 27 of 31 patient with capsule retention, the device was removed surgically and by double-balloon enteroscopy in one patient. Two of the patients still had the capsule retained after 2 years of watchful waiting. One patient with CD and a stricture had retained the capsule for 2.5 years, and with spontaneous passage occurring at that point.

Severe obstructive symptoms after CE were reported in 7 patients and appeared up to 4 weeks after the CE-examination. In 6 of the patients, intestinal obstruction with capsule retention in the affected area was confirmed radiographically, and in the remaining patient the capsule was found proximal to the obstruction.

The surgical procedures were performed as emergent or semiurgent procedures, 1-2 days after the radiographic examination in 6 patients. One patient underwent emergency surgery without a new radiologic confirmation when obstructive symptoms appeared. In all 7 patients obstructive intestinal disease was found during surgery, but in 3 of the patients no capsule was found. The clinical evaluation indicated that CE had contributed to the onset of acute obstructive symptoms in 6 of the 7 patients.

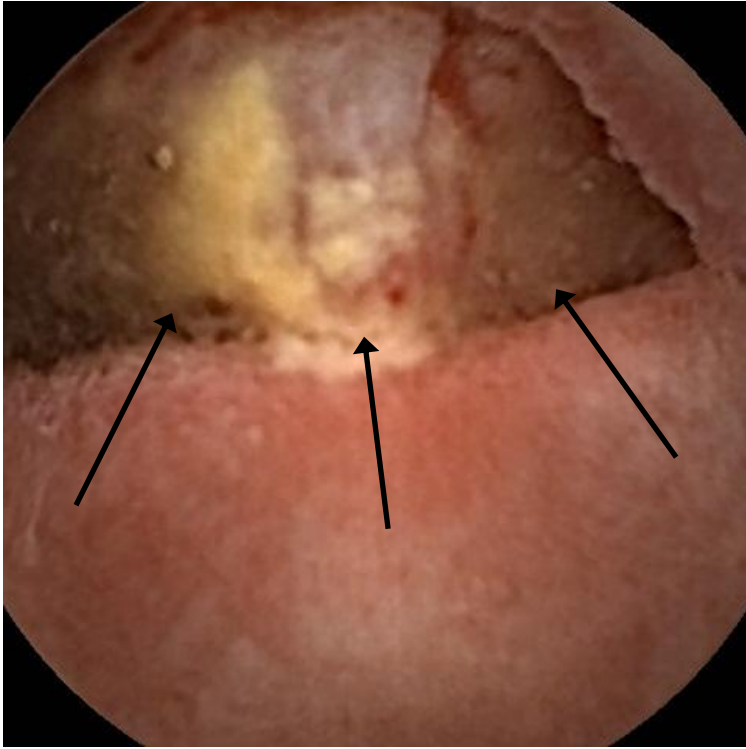
Postoperative complications were reported in 3 of 27 patients who underwent surgery; two patients died a few days postoperatively; the first from a widespread malignant disease and multiorgan failure in the intensive care unit and the second (a 53-year-old male with stricturing CD) who initially did well, had a cardiac arrest postoperative day 6. Autopsy demonstrated an anastomotic rupture.

5.4.2.2 Risk Factors for Capsule Retentions

The risk of capsule retention did not correlate with gender ($p = 0.19$) or age ($p = 0.14$). The highest risk was found in patients with previously known CD [figure 14] with an odds ratio of 9.39 (3.32–26.54, $p < 0.001$) compared with OGIB. Suspected tumor [figure 15] as an indication for CE was also associated with a higher risk of capsule retention with an odds ratio of 3.88 (1.18–12.81, $p = 0.026$).



[14] Stricturing Crohn's disease in the small bowel, image by CE.



[15] Small intestinal adenocarcinoma obstructing the lumen, image by CE.

6 DISCUSSION

Capsule endoscopy gave us the opportunity to visualize the entire small intestinal mucosa in real time view. In one aspect we do this perhaps in a better way than conventional endoscopy since the reader is just viewing – not interfering with the natural process e.g. transporting digestive content through the gastrointestinal channel. It is a fascinating journey, not always moving forward or with the camera in the front, and things do happen. The onset of bleeding can be observed for example, spontaneously or after the capsule has been pressed through a narrow passage. Massive tumors and ulcers of all sizes can suddenly appear in only one or a series of several images. In almost all examinations one can take a close look at the beautiful villi – often through clear liquid which create a coral reef-like appearance.

When first introduced CE had a high diagnostic yield ^{16, 71, 72} and this was probably partially due to case selection and also to over-diagnosing endoscopic findings. The high frequency of CE findings was somewhat surprising ^{16, 28, 72, 73}, since the small bowel had been almost discounted as a source of pathology. CE quickly gained popularity; in the first year at Södersjukhuset (2003) 25 examinations were performed, 100 in the following year and by 2008 the frequency peaked at 300. While OGIB was the only indication from the beginning it soon was used for a variety of indications like CD, refractory celiac disease and suspected small-bowel malignancy, all of which became accepted indications eventually ^{11, 31}. If patients are correctly selected for CE the diagnostic yield is still good ^{21, 35, 74}.

6.1 CE AT CID

A major concern of CE has always been capsule retention ^{62, 63, 75}. Chronic intestinal dysmotility (CID) was initially one of the few contraindications to CE ^{76, 77} – perhaps a bit of a paradox considering that these patients, if any, have already been ruled out for obstructive lesions. Starting to examine these patients with CE was more challenging due to stomach retention and a poor visualization. The results from study I failed to demonstrate significant difference between the two groups of CID as well as to a control group with regards to transit times, which may be an effect of an underpowered study. Mucosal breaks were found in 89% of the patients and this can be compared to 14% in a study of healthy individuals ⁵⁰. The impaired view in the study group (54% vs. 17% in the control group) may also have contributed to the fact that mucosal breaks were missed, indicating that the frequency of mucosal breaks could have been even higher.

The mucosa at the CID was not expected to show any mucosal breaks, the reasons for this remained unclear. Bacterial overgrowth ⁷⁸ which is common in CID as a complication of impaired transit or low-grade mucosal inflammation ⁷⁹ may partly explain this finding.

In summary CE can be performed in patients with CID. CE may be useful in selected cases of CID and when a concurrent disorder in the small intestine is suspected.

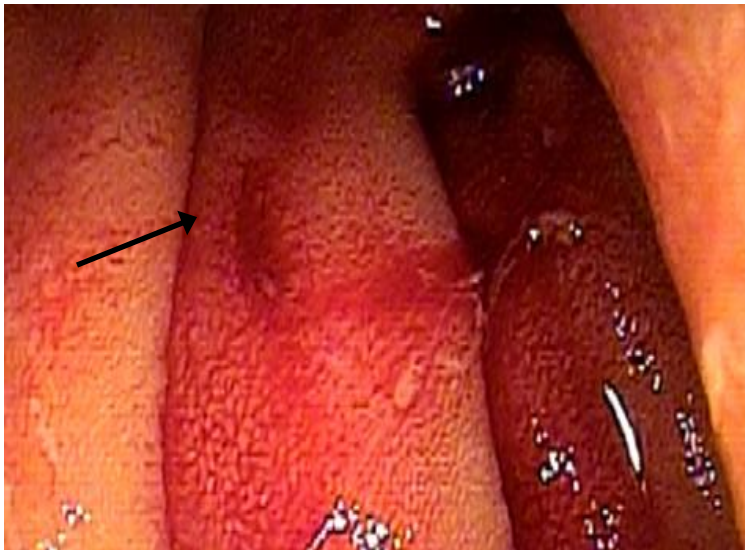
6.2 BLEEDING FROM ANGIOECTASIAS – DUE TO A BLEEDING DISORDER?

A common findings on CE is, angioectasias or a vascular malformation, which often is the bleeding source we are looking for in patients with OGIB, but can also be found in patients with no evidence of bleeding³⁷.

The aim of study II was to determine if AVWS or other bleeding disorders were associated with bleeding from angioectasias [16] compared with a control group, thus explaining the bleeding tendency and providing a basis for routine testing for hemophilias in these cases. In this study, no relationship was found between gastrointestinal bleeding from angioectasias and AVWS or any other bleeding disorder. Only hemoglobin levels differed significantly between groups. Even if a larger study group was used to determine the possible relationship between bleeding from angioectasias and a bleeding disorder, the results would at the best indicate a very weak correlation.

Why some patients bleed from angioectasias and the association with AVWS or any other coagulation disorder remains unknown. Cardiovascular disease has been shown to be a risk factor for bleeding from angioectasias⁸⁰. Advanced age is another factor that can increase the risk^{38, 81}. These results may reflect the fact that bleeding from angioectasias is caused by multiple factors, some of which remain unknown.

The clinical implications of these results indicates that there is no need for routine testing for AVWS or other bleeding disorders in patients with bleeding from gastrointestinal angioectasias. In known aortic stenosis or repeated hemorrhage, testing of VWF multimers might be considered.



[16] Bleeding from an angioectasia, image by DBE.

6.3 CE FINDINGS SUSPICIOUS FOR CD

After increasing experience with CE, suspected CD and the evaluation of known CD became a more common indication for CE²³. While new clinical information about the disease was exciting, the relevance of these findings was unknown. It is known that healthy individuals can present inflammatory lesions in up to 14%, although these lesions usually consisting of a few small erosions⁵⁰. This was the background to the design of study III where a possible correlation between CE findings of CD and other parameters of CD: symptoms, CRP, fecal calprotectin, and when possible, histopathologic diagnosis, was tested.

In clinical practice a lack of positive biopsy findings in the small bowel is not uncommon and the diagnosis is based on the remaining parameters. Thus the clinical implications of inflammatory CE findings are crucial to understand. This study demonstrated a correlation between CE findings of inflammation and laboratory inflammatory parameters, but not with gastrointestinal symptoms.

In approximately half of the patients, it was possible to achieve a histopathological diagnosis of CD. Patients confirmed with biopsy verified diagnosis of CD also had a significantly higher LS and calprotectin levels, possibly reflecting that more lesions carried a higher possibility of true CD.

HBI did not significantly correlate with endoscopic inflammation. The findings are in line with a recent published study where only a weak correlation between small bowel mucosal inflammation and HBI was shown⁶⁸. The reasons for this include the fact that HBI may not fully reflect symptoms of a purely small bowel CD and that some patients may also have suffered from irritable bowel syndrome, which is a common coexisting condition with CD^{82, 83}.

CD usually has a relapsing-remitting course and the endoscopic picture may vary over time due to the effects of medication. To confirm reliability of the data a second CE, HBI, CRP and calprotectin were performed after nine months. A correlation between the difference of LS and fecal calprotectin at inclusion and at follow up was demonstrated, indicating that CE findings and calprotectin levels remains associated also over time, further strengthening the study results. A clinical application of the results may be in the treatment of patients with small bowel CD, where tests with fecal calprotectin alone can facilitate the evaluation of these individuals. The use of fecal calprotectin as a selection tool before CE in patients with suspected CD has earlier been suggested⁸⁴ and the use is further strengthened by this study.

To conclude study III, a correlation between the severity of inflammation in the small bowel on CE and inflammatory parameters (calprotectin and CRP) was seen, whereas no correlation with symptoms was found. The results of this study may contribute to the knowledge of the validity of CE findings in small bowel inflammation.

6.4 SIX YEARS OF CE EXPERIENCE IN STOCKHOLM

After six years of practicing CE in Stockholm, study IV was performed. This consecutive study evaluated all CE investigations between June 2003 (when the first CE was performed at Södersjukhuset) to December 2009 in Stockholm County (n=2300). It showed a low rate of retention affecting, in particular, patients with known CD or suspected tumor. The overall prognosis and outcome of these patients with capsule retention due to benign disease were good although one fatality occurred due to a postoperative complication after surgical capsule retrieval.

In 20% of the CEs, the examination was incomplete (the capsule did not reach the cecum during recording time). Risk-factors for this event included known or suspected CD, advanced age, male gender and suspected small-bowel tumor. To identify patients with risk-factors and then check capsule position after one hour by means of the real time viewer, a piece of equipment that all CE systems have got today, is a way of detecting gastric retention. If the capsule after one hour still remains in the stomach there are some alternative options. A single dose of intravenous erythromycin (250 mg) can be administered which stimulates gastric emptying. As mentioned earlier, another method is to perform a gastroscopy with manual placement of the capsule in the duodenum. Although these are effective methods of avoiding gastric retention and instead get images from the small bowel, they do not seem to affect the completion rates significantly, showed in a recent meta-analysis⁸⁵. Methods for increasing the completion rate thus require improvement.

Seven of the 31 patients with capsule retention experienced obstructive symptoms, ultimately requiring emergent or semi-urgent surgery. CE most likely did contribute to the onset of acute obstructive symptoms in at least 6 of the 7 patients although the underlying disease of course was the main reason for intestinal obstruction. Obstructive symptoms due to impaction of the capsule have been reported in other studies but at a lower frequency^{35, 86, 87}. This study indicates that it is more common than previously thought.

Known CD was associated with the highest risk for capsule retention, in accordance with previous literature^{36, 63}. A suspected tumor was also shown to be a risk factor. In a large multicenter study, tumors were shown to be associated with capsule retention in 9.8% of patients⁸⁸. In the case of a stricturing tumor, the patient usually requires surgery anyway, with removal of the capsule at that time. A CD stricture could have been asymptomatic and still prevented the passage of the capsule⁶³, thus there is a risk of unnecessary surgery if the capsule has to be removed. On the other hand, CE can also be a way of finding a significant stricture that requires surgical intervention⁸⁹. The use of a patency capsule (a test capsule that dissolves after 72 hours) prior to CE⁹⁰ can lower the risk of capsule retention⁹¹ but also excludes some patients from being diagnosed by CE. Advantages and disadvantages of CE examination should be considered carefully; in particular, when high risk patients are involved. The most common means of capsule retrieval in this study was surgical; however, device assisted enteroscopy (DAE)^{86, 92} will likely be used increasingly as an alternative to surgery in the future.

7 FUTURE PERSPECTIVES

Capsule endoscopy will probably be further developed with higher resolution, longer battery times and higher image frequency. The possibility for the capsule to adjust the image frequency to the speed is already available⁹³ as well as possibilities to steer the capsule from outside of the body⁹⁴. In the future the capsule might be equipped with even more advanced features. They include tissue diagnosis capabilities such as brushing, cytology, fluid aspiration, biopsy, drug delivery, and therapeutic (coagulation) capabilities^{14, 95, 96}.

However, although CE is a very usable tool as concluded in this thesis, it has both its advantages and disadvantages. Other methods have other features and the best method should be chosen in every single case. For example; CE is the best method to evaluate the mucosa of the small bowel but to evaluate submucosal abnormalities magnetic resonance imaging will most probably be a better choice⁹⁷. In many cases it is advisable to proceed the work up after a positive CE with DAE which has the possibility to take biopsies and perform therapies⁵⁴. With DAE it is also possible to remove entrapped capsules⁹², thus avoiding unnecessary surgery. Also a good co-operation with physicians in other specialities, especially surgeons is essential. Therefore it is important that patients with small bowel disease are handled at centres with access to different imaging methods as well as endoscopic methods.

Ensuring a good care of patients with small bowel disease at centres with knowledge, experience and access to different diagnostic and therapeutic possibilities is perhaps the most important aspect of future development.

8 CONCLUSIONS OF THE THESIS

- Capsule endoscopy can be performed in patients with chronic intestinal dysmotility
- Capsule endoscopy reveals a high frequency of mucosal breaks in patients with chronic intestinal dysmotility
- Bleeding from gastrointestinal angioectasias was not shown to correlate to acquired von Willebrand syndrome
- Bleeding from gastrointestinal angioectasias was not shown to correlate to bleeding disorders
- Inflammatory lesions suspicious for Crohn's disease diagnosed by capsule endoscopy correlate with inflammatory markers in the blood and stool
- Inflammatory lesions suspicious for Crohn's disease diagnosed by capsule endoscopy do not correlated with gastrointestinal symptoms
- Incomplete examination occurs in 20% of capsule endoscopies. Risk-factors include high age, male gender, known or suspected Crohn's disease and suspected small-bowel tumor
- Capsule retention occurs in 1.3% of capsule endoscopies. Risk-factors include known Crohn's disease and suspected tumor
- Obstructive symptoms due to capsule retention are rare, but do occur and may be more common than previously thought
- *General conclusion: Capsule endoscopy provides good diagnostic information and a low risk of complications*

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

“Kapselendoskopi för diagnostik av tunntarmssjukdom” är den svenska översättningen av detta avhandlingsarbete. Tunntarmen har på grund av sitt läge i mitten av magtarmkanalen varit svåråtkomligt för undersökning tidigare. De övre och nedre delarna kommer man sedan 1970-talet åt med flexibel endoskopi, dvs en videokamera monterad i änden på en böjlig slang, men för undersökning av tunntarmen har man varit hänvisad till röntgenteknik och då inte kunnat få direkta bilder från tunntarmens insida.

Kapselendoskopi innebär att man sväljer en liten inkapslad videokamera som tar bilder under sin färd genom magtarmkanalen. Kapseln rör sig framåt med hjälp av tarmens egen rörlighet, tar kontinuerligt bilder som skickas direkt till en inspelningsutrustning som patienten bär på sig och kommer sedan på den naturliga vägen ut tillsammans med avföringen. Kapseln är av engångsmaterial och behöver inte tillvaratas efter undersökningen.

Kapselendoskopi presenterades år 2000 och har funnits tillgängligt i Sverige sedan 2002. Den har snabbt blivit populär pga sina goda möjligheter att finna sjukdom i tunntarmen och att den för patienten är en väl tolerabel undersökningsteknik.

Avhandlingens övergripande syfte var att utvärdera kapselendoskopi och dess möjligheter att ställa rätt diagnos samt att klargöra risker med tekniken.

9.1 STUDIE I: FALSKT TARMVRED

I det första arbetet fick patienter med falskt tarmvred, genomgå kapselendoskopi. Falskt tarmvred, även kallad ”pseudoobstruktion”, är en ovanlig men fruktad, inte fullständig klarlagd magtarmsjukdom som orsakar svår magsmärt, kräkningar och avföringsrubbningar. Kapselendoskopitekniken var inte prövad på denna patientgrupp tidigare.

Vi fann tecken på att tarmrörelserna fungerade undermåligt hos dessa patienter, vilket var känt sedan tidigare, men när man jämförde tiden det tog för kapseln att ta sig igenom tunntarmen, var den inte förlängd jämfört med en kontrollgrupp. Vad som var nytt var att vi såg små förändringar, liknande skrapår och även en del större sår i slemhinnan i en betydligt högre utsträckning än vad som kunde förväntas. Orsaken till detta kunde vi inte förklara med vår studie. Vi kunde dock konstatera att kapselendoskopi är möjligt att utföra i denna patientgrupp.

9.2 STUDIE II: BLÖDNING FRÅN KÄRLFÖRÄNDRINGAR

I det andra arbetet tittade vi närmare på kärlförändringar i tarmslemhinnan. Dessa så kallade ”angiektasier” är tvärkopplingar mellan grövre blodkärl. I dessa kan blodet rinna med hög hastighet samtidigt som väggen är tunn. Angiektasier anses vara orsakat av åldrandeprocessen i kärlsystemet men uppstår av oklar orsak bara hos vissa individer. I en del fall kan dessa blöda kraftigt och orsaka både synlig och ej synlig blödning samt blodbrist. Angiektasier är ett av de vanligare fynd som kapselendoskopi påvisar när man letar efter orsak till blödning i tunntarmen. Syftet med studie II var att finna förklaring till varför vissa personer blöder från sina angiektasier. Därför testades en patientgrupp med angiektasiblödning för ett flertal blödningssjukdomar där särskilt fokus ägnades åt förvärvad von Willbrands sjukdom, vilken tidigare anklagats för att vara en orsak till dessa blödningar. Resultaten jämfördes med personer från en kontrollgrupp utan angiektasier. Endast blodvärdet kunde påvisas vara lägre i studiegruppen, de övriga resultaten visade ingen statistisk skillnad mellan grupperna. Slutsatsen vi drog var då att man inte rutinmässigt behöver utföra blödningstester på patienter som blöder från angiektasier.

9.3 STUDIE III: CROHNS SJUKDOM

I det tredje arbetet undersökte vi hur pass säker kapselendoskopi är på att diagnostisera Crohns sjukdom. Crohns sjukdom är en så kallad inflammatorisk tarmsjukdom där kroppens eget immunförsvar går till attack med den egna slemhinnan. Detta yttrar sig i smärtor, blödningar och diarréer. Man kan även drabbas av förträngningar i tarmen. Vid kapselendoskopi ser man sår, svullen slemhinna och ibland trånga partier. Problemet kan dock vara att det finns även andra sjukdomar som uppvisar en liknande bild. När Crohns sjukdom uppkommer i magsäck eller tjocktarm är det relativt enkelt att ta små provbitar för mikroskopisk analys vid vanlig endoskopi. Men detta klarar inte kapseln av.

Vi har därför i studie III jämfört de inflammatoriska förändringar, som vi via kapseln ser i tunntarmen hos patienter där vi misstänker Crohns sjukdom, med andra parametrar i blod (CRP) och avföring (calprotektin) som också talar för Crohns sjukdom. Om de är korrelerade bör detta kunna stärka misstanken om att det är just Crohns sjukdom som kapselendoskopibilderna visar. Vi jämförde också svårighetsgraden av inflammation i bilderna med svårighetsgraden av patienternas symtom.

Resultatet visade att det finns ett starkt samband mellan de inflammatoriska förändringar vi ser vid kapselendoskopi och calprotektin, ett något svagare men signifikant samband med CRP men inget samband alls med patientens besvär. Detta stärker kapselendoskopins roll vid diagnos av Crohns sjukdom i tunntarmen, men man måste lägga samman all information och sträva efter att få provbitar för mikroskopisk undersökning när så är möjligt. Att inflammationsgraden inte hänger ihop med patientens besvär kan nog förvåna en del. Men det är egentligen vad man ständigt konstaterar som praktiserande läkare inom magtarmspecialiteten (och troligen andra specialiteter också); det största såret är inte nödvändigtvis det som gör mest ont – det är så många faktorer som spelar in.

9.4 STUDIE IV: UTVÄRDERING AV 2300 KAPSELUNDERSÖKNINGAR

Den fjärde och sista studien är en tillbakablickande studie där vi samlade information från alla kapselendoskopiundersökningar som gjorts i Stockholm sedan starten 2003. Det rör sig om 2300 stycken och de är utförda på fyra olika sjukhus. Majoriteten av undersökningarna är dock gjorda på Södersjukhuset och Karolinska Huddinge sjukhus.

Den vanligaste orsaken till att kapselendoskopi utförts var misstänkt blödningskälla i tunntarmen. Andra orsaker var misstänkt Crohns sjukdom, kartläggning av Crohns sjukdom och misstänkt tumör.

I 20% av fallen kunde inte hela tunntarmen undersökas pga att kapseln av olika skäl färdades för långsamt genom tunntarmen och inte hann igenom innan undersökningen var slut.

Patienter som undersöktes pga misstänkt eller känd Crohns sjukdom eller misstänkt tumör hade en högre risk än andra för ofullständig undersökning. Ålder och kön påverkade också.

I 1,3% av patienterna, dvs 31 stycken blev kapseln kvar i tunntarmen pga förträngningar.

Dessa var orsakade av strålningsskador, Crohns sjukdom eller tumörer. Tjugosju stycken patienter fick genomgå operation för att avlägsna kapseln. I de flesta fall, dock inte alla, skulle patienten ändå genomgå operation för den sjukdom som kapseln nu hade funnit. Sex patienter fick smärtor av att kapseln trängde på i tunntarmen och fick opereras akut.

Sammantaget konstaterades att kapselendoskopi är en undersökningsmetod med goda möjligheter att finna sjukdomstillstånd i tunntarmen, med låg men inte obefintlig risk för komplikationer.

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After a side-step into the world of anesthesiology, I was back on track in 2002 when I started of as a resident physician in Gastroenterology and Hepatology at Södersjukhuset. Already in 2003 I was introduced to a new technique for examining the small bowel; *capsule endoscopy* and also offered to learn to work with it. As you readers may have realized now, this was actually before I could manage the basic technique of ordinary gastrointestinal endoscopy. This might not be the learning sequence that I would recommend for other residents, but reflects that things can be done in more than one way.

Eventually capsule endoscopy and small bowel diseases became the theme of my research work which led to this thesis.

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12 ORIGINAL PAPERS