Perception of reflux and mucosal integrity in the proximal oesophagus

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Key objective: the hypothesis that will be tested:Our hypothesis is that the proximal oesophagus of patients with GORD is more sensitive to acid than the distal oesophagus, which is due to more pronounced mucosal integrity changes in the proximal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Observational invasive

Summary

ID

NL-OMON38752

Source
ToetsingOnline

Brief title
Proximal oesophageal sensitivity

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
GORD, Reflux disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: mucosal integrity, proximal esophagus, reflux disease, reflux perception

Outcome measures

Primary outcome

Oesophageal sensitivity represented by the perfusion sensitivity score

Secondary outcome

• Transepithelial permeability to small molecules

• Transepithelial resistance of oesophageal mucosa

• Extracellular impedance measured in vivo with ETIS

Study description

Background summary

Gastro-oesophageal reflux disease
Approximately 15-20% of the general population experiences heartburn and/or regurgitation at least weekly (1). Although it is generally accepted that gastro-oesophageal reflux causes these symptoms, the mechanism through which this occurs has not been clarified. In the minority of patients mucosal abnormalities such as oesophagitis can be found during upper endoscopy, these patients suffer from erosive reflux disease (ERD). However, the vast majority of patients has no mucosal abnormalities during upper endoscopy and thus suffers from so-called non-erosive reflux disease (NERD). Regardless of the presence of distal erosions all GORD patients seem more sensitive during oesophageal acid infusion compared to asymptomatic controls (2,3). The cause of this hypersensitivity to acid is unclear.

Proximal extent of reflux and proximal oesophageal sensitivity to acid
Several studies have demonstrated that patients with reflux disease have more proximal reflux episodes than healthy controls.(2,4) Furthermore, reflux that reached the proximal oesophagus more often generated typical reflux symptoms than reflux that only reached the distal oesophagus.(5) Also, in patients with reflux symptoms despite PPI therapy reflux episodes reaching the proximal oesophagus were more often associated with symptoms than reflux reaching only the distal part of the oesophagus.(6,7) A study using multiple pH-impedance sensors at different oesophageal levels showed that the proportion

of both acidic and weakly acidic reflux episodes that become symptomatic is significantly higher in the proximal oesophagus than in the distal oesophagus.(8) These data suggest that the proximal oesophagus is more sensitive to acid than the distal oesophagus.
Oesophageal sensitivity to acid can be measured using an acid perfusion test. A neutral and an acidic solution are perfused in the oesophagus in a random order while the patient is blinded to the nature of the solution. Subsequently, the time to heartburn perception and the intensity of perceived heartburn is scored. Our group recently showed that patients with non-erosive reflux disease are more sensitive to distal acid perfusion than healthy subjects. (Weijenborg et al., UEGW 2012) However, the sensitivity of the proximal oesophagus measured with an acid perfusion test has not been separately assessed.

Oesophageal mucosal integrity
The oesophageal mucosa is characterized by the presence of a non-keratinised squamous epithelium, forming an effective barrier against noxious substances during the reflux of gastric contents. The integrity of this barrier is impaired in patients with reflux disease, demonstrated by the presence of dilated intercellular spaces and increased transepithelial flux of small molecules.(9,10) Recently our group demonstrated that these mucosal integrity parameters were related to acid hypersensitivity measured by an acid perfusion test. (Weijenborg, UEGW 2012). Patients with an impairment of mucosal integrity are characterized by an increase in esophageal sensitivity to acid.
In the present study we will evaluate the sensitivity of different regions of the oesophagus. We will investigate whether the proximal oesophagus is more sensitive to acid by separate infusions of these regions during an acid perfusion test. We will also investigate whether mucosal integrity changes underlie these changes in sensitivity by doing in vivo and in vitro mucosal integrity measurements.

Study objective

Key objective: the hypothesis that will be tested:
Our hypothesis is that the proximal oesophagus of patients with GORD is more sensitive to acid than the distal oesophagus, which is due to more pronounced mucosal integrity changes in the proximal oesophagus.
This can be further specified:
• Lag time to heartburn perception is shorter after proximal acid perfusion compared to distal acid perfusion.
• Heartburn intensity is higher after proximal acid perfusion compared to distal acid perfusion.
• Impairment of the mucosal barrier after acid perfusion is larger in the proximal esophagus than in the distal esophagus, which is characterized by a:
o Lower in vivo impedance of tissue
o Lower in vitro transepithelial electrical resistance
o Higher in vitro transepithelial permeability of small molecules
o Larger intercellular spaces

• A positive relation between acid perception and mucosal barrier impairment

Aim
To investigate the segmental sensitivity to acid of the oesophagus in patients with GORD and its underlying mechanism.

Study design

The study has a prospective observational design and the protocol consists of a single acid perfusion test and obtaining electrical tissue impedance measurements and mucosal biopsies during a routinely planned gastroscopy. The MEC of the AMC Amsterdam has previously granted permission for the inclusion of GORD patients and healthy volunteers in a similar protocol (MEC10/275).

Study burden and risks

The risk of the performed procedures consists of the risk related to obtaining oesophagal biopsies. Oesophageal biopsies are taken regularly during upper endoscopy. A very rare but potentially severe risk of a biopsy is a perforation. In the vast majority of cases perforation can be treated expectative or endoscopically. In a minority of cases, surgery has to be performed to close the perforation. Another very rare risk of an oesophageal biopsy is bleeding, which can be treated endoscopically.
The acid perfusion test is a safe procedure, only associated with discomfort during placement of the perfusion cathether. There is no additional risk involved with the tissue impedance measurements. The extra procedures during endoscopy will proong the time of a regular endosocpy with 3-4 minutes. The study will contribute to better understanding of the condition and possibly offer new targets of treatment.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1100 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1100 AZ

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients with heartburn lasting more than 12 months
- A 24-hour pH-measurement showing a symptom association probability > 95%
- Written informed consent
- Age 18 - 75 years

Exclusion criteria

- Barrett*s oesophagus
- History of GI cancer
- GI tract surgery (except appendectomy)
- Inability to stop PPI, H2-receptor antagonist or prokinetic drug for 10 days

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-07-2013
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO

Date:	20-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL42915.018.12