UMF
UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE IULIU HAȚIEGANU CLUJ-NAPOCA

Teză de doctorat

“Monitorizarea refluxului gastroesofagian cu ajutorul impedanţ-pH metriei”

“Monitoring gastroesophageal reflux disease using combined impedance-pH-metry”

Rezumat

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Cuprins

Cuvinte cheie

boala de reflux gastroesofagian
pirozis
endoscopia digestivă superiora
pH-metria esofagiană
impedanţ-pH metria esofagiana
inhibitori de pompă protonică
chirurgia anti-reflux

Boala de reflux gastroesofagian este o boală cronică cu o prevalenţă ridicată. În Statele Unite ale Americii 40% din populaţia adultă se plânge de pirozis, simptomul principal al bolii de reflux gastroesofagian. Comparat cu celelalte boli ale tractului digestive, boala de reflux se situază pe locul patru in ordinea frecvenţei şi este boala gastrointestinală cu cel mai înalt impact financiar asupra sistemului sanitar. Manifestările clinice ale bolii de reflux includ simptome tipice (i.e. pirozis, regurgitări) si simptome atipice (i.e. dureri retrosternale, tuse, atacuri astmatice, laringită, etc.). Inhibitorii de pompă protonica (IPP) au fost introduşi în armamentariul farmacologic de tratament al bolii de reflux la mijlocul aniilor 1980 şi sunt în momentul actual cele mai potente medicamente care suprimă secreţia de acid gastrică. Fiind accesibili în întreaga lume, IPP au schimbat nu numai evoluţia naturală şi complicaţiile bolii de reflux gastroesofagian, dar şi modalităţile diagnostice utilizate în boala de reflux.

Partea generală este structurată în patru capitole. Capitolul 1 se referă la epidemiologia şi cursul natural al bolii de reflux gastroesofagian, capitolul 2 discută patogeneza şi factorii de risc ai bolii de reflux gastroesofagian, capitolul 3 prezintă testele diagnostice şi capitolul 4 opţiunile terapeutice pentru pacienţii cu boală de reflux gastroesofagian.

Partea de cercetare personală include şase studii cu tematicile: (1) investigarea abilităţii impedanţ-metriei de a detecta şi caracteriza prezenţa fluidelor in esofag, (2) investigarea abilităţii impedanţ-pH-metriei de detecta episoadele de reflux în perioada post-prandială sub tratament cu IPP, (3) investigarea refluxului post-prandial sub tratament cu baclofen, (4) stabilirea valorilor normative pentru impedanţ-pH-metria in condiţii ambulatorii, (5) evaluarea proporţiei pacienţilor cu simptome asociate cu reflux acid şi non-acid sub tratament cu IPP şi (6) compararea caracteristicilor episoadelor de reflux simptomatice si nesimptomatice sub tratament cu IPP.

Primul project (**1st study**) constă într-un studiu de investigare a influenţei volumului, consistenţei, temperaturii şi acidităţii fluidelor asupra tranzitului esofagian într-un grup de 10 voluntari. Parametrii măsuraţi includ timpul de transit esofagian (TTE) definit ca timpul scurs între apariţia bolusului la 20cm şi eliminarea bolusului la 2cm deasupra sfincterului esofagian inferior şi viteza undei peristaltice (VUP) pe intreaga lungime a esofagului (între 20cm şi 2cm proximal sfincterului esofagian inferior). În setul de experimente din acest studiu am observat valori similare ale TTE si VUP pentru volume de apă între 1ml şi 20ml. În schimb am observat o

creştere liniară a TTE cu volume crescând de alimente semisolide şi TTE mai lungi pentru semisolide comparat cu lichide. Alimentele solide (marshmallow) au prezentat de asemenea o creştere liniară a TTE paralel cu creşterea volumului bolusului şi TTE prelungite comparat cu valorile măsurate pentru lichide. Timpul de transit esofagian nu a fost influenţat de temperatură. Alimentele semisolide au fost acompaniate de unde peristaltice cu viteză descrescătoare paralel cu creşterea volumului bolusului. Valori descrescătare ale VUP au fost observate paralel cu creşterea volumului alimentelor solide. Reflucerea temperaturii lichidelor a condus la o reducere simnificativă a VUP. Sumarizând observaţiile acestor experimente putem afirma că volumul lichidelor nu influenţează timpul de transit esofagian, în schimb volumul alimentelor semisolide şi solide afectează timpul de transit esofagian şi viteza undei peristaltice esofagiene. Bazat pe observaţiile acestui studiu am concluzionat ca măsurătoriile de impedanţă intraesofagiană pot fi folosite pentru caracterizare prezenţei fluidelor în esofag.

În al 2-lea proiect am evaluat utilizarea combinaţiei impedanţ-metrie şi pH-metrie (imp-pH) pentru detectarea refluxului gastroesofagian. În primul pas (**2nd study**) am comparat refluxul gastroesofagian în perioada post-prandială în condiţii naive şi după o săptămână de tratament cu omeprazol 20mg de două ori pe zi. Doisprezece pacienţi cu boala de reflux au fost monitorizaţi pentru 2 ore după ingestia unui meniu refluxogen (meniu McMuffin – McDonald; 60% grăsimi şi 250ml cafea) în poziţie de decubit lateral drept pentru a maxima şansele de apariţie a refluxului gastroesofagian. Acest scenariu de monitorizare post-prandială timp de 2 ore a fost repetat odată in condiţii naive şi a doua dată după o săptămână de tratament cu IPP. În acest experiment am observat o reducere semnificativă a numărului de episoade de reflux gastroesofagian acid (i.e. epidsoade detectate de impedanţ-metrie cu un pH<4) sub tratament cu IPP, în schimb numărul total de episoade de reflux detectate de impedanţ-metrie a rămas neschimbat sub tratment cu IPP. Deşi un număr mai mare de simptome a fost asociat cu episoade de reflux acid, un număr important de episoade de reflux non-acid (i.e. epidsoade detectate de impedanţ-metrie cu un pH>4) au fost asociate temporar cu simptome, în particular cu senzaţia de regurgitaţie. Aceste rezultate sugerează că simptomele de reflux gastroesofagian pot fi declanşate de prezenţa refluatului sau de modificări în osmolalitate în esofag.

În al doilea pas (**3rd study**) am comparat refluxul gastroesofagian post-prandial intr-un grup de voluntari sănatoşi şi un grup de pacienţi cu boală de reflux gastroesofagian sub tratament cu placebo sau baclofen 40mg administrate intr-un design dublu-orb. Baclofen, un medicament utilizat în tratamentul bolilor spastice musculare, este un agonist al receptorilor B ai acidului gama-amino butiric care reduce frecvenţa relaxărilor transiente ale sfincterului

esofagian inferior. Deoarece relaxările transiente ale sfincterului esofagian inferior sunt un mecanism important în patogeneza refluxului gastroesofagian, ipoteza acestui studiu a fost că un medicament capabil să reduca relaxările transiente va conduce la o reducere a frecvenţei tuturor episodelor de reflux gastroesofagian. Datele colectate în 9 voluntari sănătoşi şi 9 pacienţi cu boală de reflux gastroesofagian indică o reducere semnificativă al numărului de episoade de reflux acid, non-acid şi implicit al numărului total de episoade de reflux gastroesofagian sub tratament cu baclofen 40mg comparativ cu placebo. Aceste date confirmă ipoteza conform căreia medicamente care reduc relaxările transiente ale sfincterului esofagian inferior, pot fi utilizate in controlul refluxului gastroesofagian acid şi non-acid.

Date normative pentru monitorizarea refluxului gastroesofagian cu ajutorul impedanţ-pH metriei (**4th study**) au fost stabilite în cadrul unui studiu multicentric implicând 4 centre din SUA (Graduate Hospital Philadelphia, Cleveland Clinic, Mayo Clinic Rochester şi University of South California, Los Angeles) şi un centru european (KU Leuven, Belgia). Voluntari sănătoşi, fără simptome esofagiene au fost investigaţi cu impedanţ-pH metrie utilizând un cateter cu segmente de măsurare a impedanţei localizate 3, 5, 7, 9, 15 şi 17 cm şi un sensor de pH localizat 5 cm deasupra marginei proximale a sfincterului esofagian inferior. Rezultatele obtinuţe în acest grup de voluntari sănătoşi documentează că, în absenţa unui tratament supresive gastric, episoadele de reflux gastroesofagian cu un pH >4 (i.e. „slab acid" sau non-acid) sunt mult mai rare comparativ cu episoadele de reflux acid şi apar în principal în perioadele post-prandiale. Acest set de date ne-a permis stabilirea unor valori normale pentru diverşi parametrii detectaţi de impedanţ-pH metrie (data bazate pe a 95-ea percentilă a valorilor registrate în acest grup de volunari sănătoşi).

În continuarea acestui studiu am preluat conducerea unui studiu multicentric (American-Belgian) incluzând 168 de pacienţi cu simptome de reflux persistente sub tratament supresive al secreţiei gastrice (**5th study**). Evaluând pacienţi cu simptome tipice si atipice sub tratament cu IPP de două ori pe zi ± antagonisti de receptori de histamină H2 am investigat proporţia de pacienţi cu indice simptomatic positiv (i.e. cel putin 50% din simptome precedate de un episod de reflux gastroesofagian). Raportat la întergul grup de pacienţi 11% au avut un indice simptomatic positiv pentru reflux acid, 37% un indice simptomatic positiv pentru reflux non-acid şi 52% un indice simptomatic negativ. În subgrupa de 82 de pacienţi cu simptome tipice de reflux 10% au avut un indice simptomatic positiv pentru reflux acid, 45% un indice simptomatic positiv pentru reflux non-acid şi 45% un indice simptomatic negativ. În subgrupa de 62 de pacienţi cu simptome atipice de reflux 2% au avut un indice simptomatic positiv pentru reflux acid, 23% un indice simptomatic positiv pentru reflux non-acid şi 75% un indice simptomatic

negativ. Aceste rezultate subliniază importanţa monitorizării episoadelor de reflux non+acid în pacienţii cu simptome persistente sub terapie cu IPP, independent dacă simptomele sunt tipice sau atipice pentru reflux gastroesofagian. Proporţia ridicată de pacienţi cu simptome asociate cu reflux non-acid subliniază limitele pH-metriei convenţionale, detectarea numai a episoadelor de reflux cu pH <4 lăsând deschisă discuţia simptomelor asociate cu reflux non-acid versus simptomelor prezente independent de reflux gastroesofagian intr-un număr important de pacienţi.

În ultimul proiect prezentat în prezenta lucrare (**6th study**) am analizat caracteristicile episoadelor de reflux simptomatice şi asimptomatice în 120 de pacienţi cu simptome persistent sub tratament cu IPP. Monitorizarea cu ajutorul impedanţ-pH metriei a permis characterizarea compoziţiei chimice (acid vs. non-acid), proprietăţilor fizice (lichid, gaz, mixt gaz+lichid), extensia proximală (esofagul distal vs. esofagul proximal), durata prezenţei refluatului (clearance-ul refluatului) şi durata timpului cu pH <4 a epidsoadelor de reflux gastroesofagian. Episoadele de reflux gastroesofagian au fost considerate simptomatice dacă pacienta/pacientul a inregistrat un simptom într-un interval de timp de 5 minute următor episodului de reflux. Utilizând modele statistice uni- şi multivariante am identificat că, deşi 87% din episoadele de reflux gastroesofagian sub terapie cu IPP sunt asimptomatice, extensia proximală şi conţinutul de gaz al episoadelor de reflux lichide contribuie mai mult decât aciditatea refluatului la percepţia acestor episoade de reflux gastroesofagian. Pe baza acestor observaţii am concluzionat că viitoarele tratamente ale episoadelor de reflux simptomatice sub terapie cu IPP vor trebui să ţintească extensia proximală şi proprietăţile fizice ale refluatului.

În rezumat monitorizarea refluxului gastroesofagian cu ajutorul impedanţ-pH-metriei oferă abilitatea de a identifica şi caracteriza toate episoadele de reflux prin detectarea prezenţei lichidelor in esofag şi separarea acestora in acid şi non-acid be baza unor criterii prestabilite. Valori normative pentru această metodă au fost stabilite pe baza datelor culese în voluntari sănătoşi. Datele culese la pacienţii cu simptome persistente sub tratament cu IPP documentează că in majoritatea pacienţilor simptomele sunt asociate cu episoade de reflux cu un pH>4 (i.e. „slab acid” sau non-acid). Chiar dacă majoritatea episoadelor de reflux non-acid sunt asimptomatice, compoziţia fizică a refluatului şi extensia proximală a refluatului sunt principali contributori la percepţia refluxului gastroesofagian sub tratement cu IPP.

În concluzie, abilitatea de detecta şi caracteriza refluxul gastroesofagian cu ajutorul impedanţ-pH metriei este valabilă in practica curentă şi oferă baza pentru dezvoltarea a noi metode terapeutice pentru pacienţii cu boală de reflux gastroesofagian.

Curriculum vitae

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07/03–07/05	Medic rezident, supraspecializare gastroenterologie şi hepatologie la Universitatea de Medicină a Carolinei de Sud, Charleston SC, SUA
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1989-1990	Serviciul miliar (sanitar medical) în România
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Keywords

gastroesopahgeal reflux disease
heatburn
upper gastrointestinal endoscopy
esophageal pH monitoring
esophageal impedance-pH monitoring
proton pump inhibitors
anti-reflux surgery

Gastroesophageal reflux disease (GERD) is a highly prevalent chronic condition. In the United States 40% of adults complain of heartburn, the hallmark symptom of GERD. Reflux disease is the 4th most common gastrointestinal disease and the gastrointestinal disease with the highest financial burden on the health system. Clinical manifestation of GERD include typical (i.e. heartburn, regurgitation) and atypical symptoms (i.e. chest pain, cough, asthma, hoarseness, sore throat, etc.). Proton pump inhibitors (PPI) have been introduced in clinical practice mid 1980ies and are currently the most potent pharmacologic agents to suppress gastric acid secretion. The natural history of GERD has been changed as PPI's are widely available and used early in the course of the disease.

The general part on current knowledge in the field is structured in four chapters. Chapter 1 discusses epidemiology and natural history of GERD, chapter 2 the pathophysiology of GERD, chapter 3 diagnostic tools and chapter 4 treatment options for GERD

The part of personal research includes six studies with the aims (1) to evaluate the ability of multichannel intraluminal impedance to detect and characterize bolus presence in the esophagus (2) to test the ability of combined impedance-pH monitoring to identify gastroesophageal reflux episodes in the post-prandial period, (3) to investigate post-prandial reflux on and off therapy with baclofen, (4) to establish normal values for ambulatory 24-h combined impedance-pH monitoring, (5) to evaluate the proportion of patients with symptoms associated with acid and non-acid reflux on acid suppressive therapy and (6) to compare the characteristics of symptomatic and asymptomatic reflux episodes on and off acid suppressive therapy.

The initial step (**1st study**) was to perform a study aimed at characterizing the influence of volume, bolus size, consistency, temperature, acidity on intraesophageal bolus transit using multichannel intraluminal impedance in 10 healthy volunteers. We measured the esophageal bolus transit time (BTT) as the time elapsed between bolus entry at 20cm and bolus exit at 2cm above the lower esophageal sphincter (LES) and the contraction wave velocity (CWV) as the speed (cm/sec) of the contraction wave over the entire length of the esophagus (20 to 2 cm above the LES). In this set of experiments we found no difference in BTT or CWV for all water volumes ranging from 1 to 20 ml. We noticed a significant linear increase of BTT with

progressively larger volumes of applesauce, and longer BTT for applesauce compared to water. Large marshmallows had longer BTT compared to small and medium marshmallows and longer BTT com-pared to water. The temperature of water had no influence on BTT. Applesauce had a significant linear decrease of CWV with progressively larger volumes and was slower than water. Marshmallow showed significantly slower CWV with the large vs. small, and CWV for ice water was significantly slower than 54°C water. Summarized, we found that the bolus transit time for liquids was independent of the volume whereas bolus transit times of semisolids and solids were volume dependent and longer than for liquids. Based on these findings we concluded that MII can be used as a discriminating test of esophageal function.

We then evaluated the use of combined MII-pH testing in gastroesophageal reflux monitoring. In one study (**2nd study**) we compared postprandial gastroesophageal reflux patterns on and off acid suppressive therapy using omeprazole 20mg twice daily. Monitoring 12 GERD patients for 2-hours after ingesting a refluxogenic meal (i.e. a sausage and egg McMuffin (McDonald's; 60% fat) with an 8-oz cup of coffee) in the right lateral decubitus position we found that PPI bid decreased the number of acid reflux episodes (i.e. MII-detected reflux episodes with a pH<4), while the total number of MII-detected reflux episodes remained the same before and after PPI treatment. While symptoms were more likely associated with acid reflux, there were a few non-acid reflux episodes (i.e. MII-detected reflux episodes with a pH>4) temporally associated with reflux symptoms. These data suggest that reflux symptoms could be triggered by the presence of volume or changes in osmolality in the oesophagus.

In a following study (**3rd study**) we compared postprandial reflux patterns in a group of healthy volunteers and GERD patients receiving either baclofen 40mg or placebo in a double-blind cross-over design. Baclofen, a pharmacologic agent typically used to treat muscular spastic disorders, is a gamma-amino butyric acid (GABA) receptor B agonist known to decrease the frequency of transient lower esophageal sphincter relaxations (TLESRs). Since TLESRs are a major mechanism of gastroesophageal reflux our hypothesis was that a pharmacologic reduction of the frequency of TLESRs should decrease the frequency of all types of reflux episodes. Data in the 9 healthy volunteers and 9 GERD patients showed a statistically significant reduction in the number of acid, non-acid and implicitly all reflux episodes when subjects received baclofen compared to when they received placebo. This data suggest that agents controlling TLESRs can be used to control both acid and non-acid reflux.

We participated in a multicentre study aimed at establishing normal values for ambulatory MII-pH monitoring (**4th study**). A total of 60 healthy volunteers recruited at 4 US (Graduate

Hospital, Philadelphia, Cleveland Clinic, Cleveland, Mayo Clinic Rochester and University of Southern California, Los Angeles) and one European (KU Leuven, Belgium) centres. Healthy volunteers not complaining of esophageal symptoms were monitored for 24-h using an MII-pH catheter with impedance measuring segments at 3, 5, 7, 9, 15 and 17cm above the manometrically located LES and an antimony pH sensor at 5cm above the LES. The results in this group of healthy volunteers indicated that, off acid suppressive therapy, gastroesophageal reflux with a pH>4 (i.e. “weakly acidic” or non-acid) occurs less frequent compared to acid reflux and established normal values for all the types of reflux detected by MII.

We took the lead of an US-Belgian multicenter study in 168 patients with persistent symptoms on acid suppressive therapy (**5th study**). Monitoring patients with typical and atypical reflux symptoms on PPI bid ± H2RA qhs we found a positive symptom index (SI) for acid reflux in 11% of patients, a positive SI for non-acid reflux in 37% of patients and a negative symptom index in 52% of patients. In the 82 patients with typical reflux symptoms 45% had a positive SI for non-acid reflux, 10% had a positive SI for acid reflux while 45% of patients with typical reflux symptoms on acid suppressive therapy had a negative SI. In the 62 patients with atypical symptoms 75% had a negative symptom index, 23% a positive SI for non-acid reflux and 2% a positive SI for acid reflux. These findings underscored the necessity of monitoring for non-acid reflux in patients with persistent symptoms on acid suppressive therapy as pH monitoring alone would not have allowed us to distinguish patients in whom reflux episodes with a pH >4 are associated with symptoms from those in whom symptoms are not associated with any type of reflux.

Data collected in patients investigated for persistent symptoms on acid suppressive therapy were analyzed for characteristics of symptomatic vs. asymptomatic reflux episodes (**6th study**). Patients underwent combined impedance-pH monitoring while on PPI bid ± H2RA qhs allowing detecting all reflux episodes and characterizing their chemical composition (acid vs. non-acid), physical properties (liquid, gas, mixed), proximal extent (distal vs. proximal esophagus), bolus clearance and acid clearance times. Reflux episodes were considered symptomatic if patients recorded a symptom within 5 minutes following the reflux episode. Using uni- and multivariant generalized estimating equation models we found that while the majority (87%) of reflux episodes on PPI therapy are asymptomatic, the proximal extension and gas content of liquid reflux, more than the acid content, play an important role in the perception of gastroesophageal reflux episodes. Based on these observations we concluded that characteristics of symptomatic reflux episodes are important in developing new therapeutic approaches for patients with symptomatic reflux episodes on acid suppressive therapy.

In summary combined impedance-pH monitoring reliably identifies and characterizes all gastroesophageal reflux episodes by detecting bolus presence in the esophagus. Normal values were established based on data collected in healthy volunteers and data in patients with persistent symptoms on acid suppressive therapy indicates that the majority of these patients have non-acid (volume) reflux episodes associated with their symptoms. While the majority of reflux episodes on acid suppressive therapy are asymptomatic, composition of the refluxate and proximal extent play an important role in the perception of reflux episodes.

In conclusion, the ability to identify and characterize gastroesophageal reflux episodes using combined impedance-pH monitoring is available in clinical routine and provides us the basis to design novel approaches for therapies in patients with gastroesophageal reflux disease.

Curriculum vitae

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American Gastroenterology Association – Member

American Medical Association – Associate Member

Swiss Medical Association (FMH) – Member

Swiss Gastroenterology Association (SGG) - Member

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Romanian – native language

German (incl. Swiss German dialect) – fluent

English – fluent

French – basic knowledge